DYSLIPIDAEMIAS: ApoB a common denominator?

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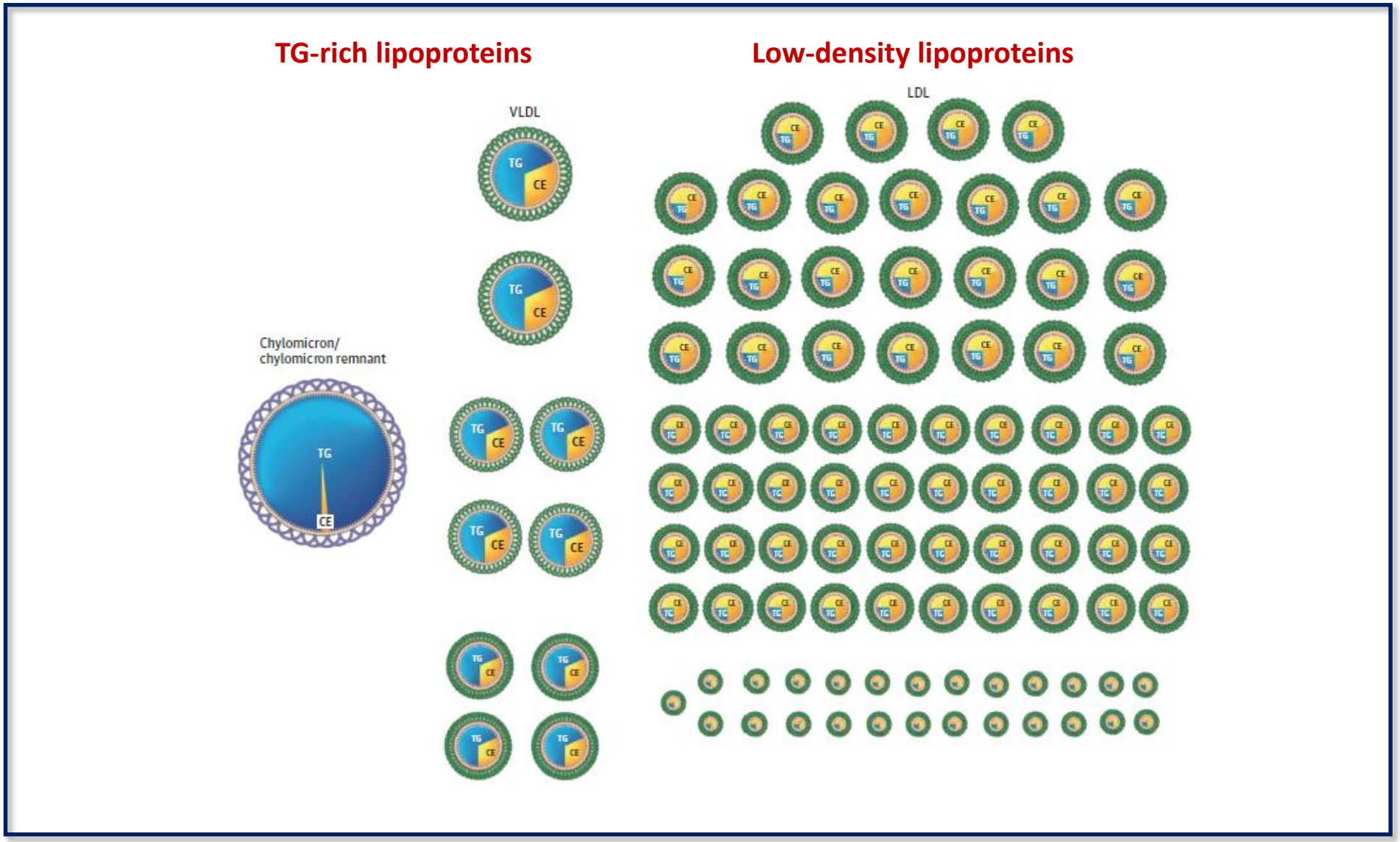
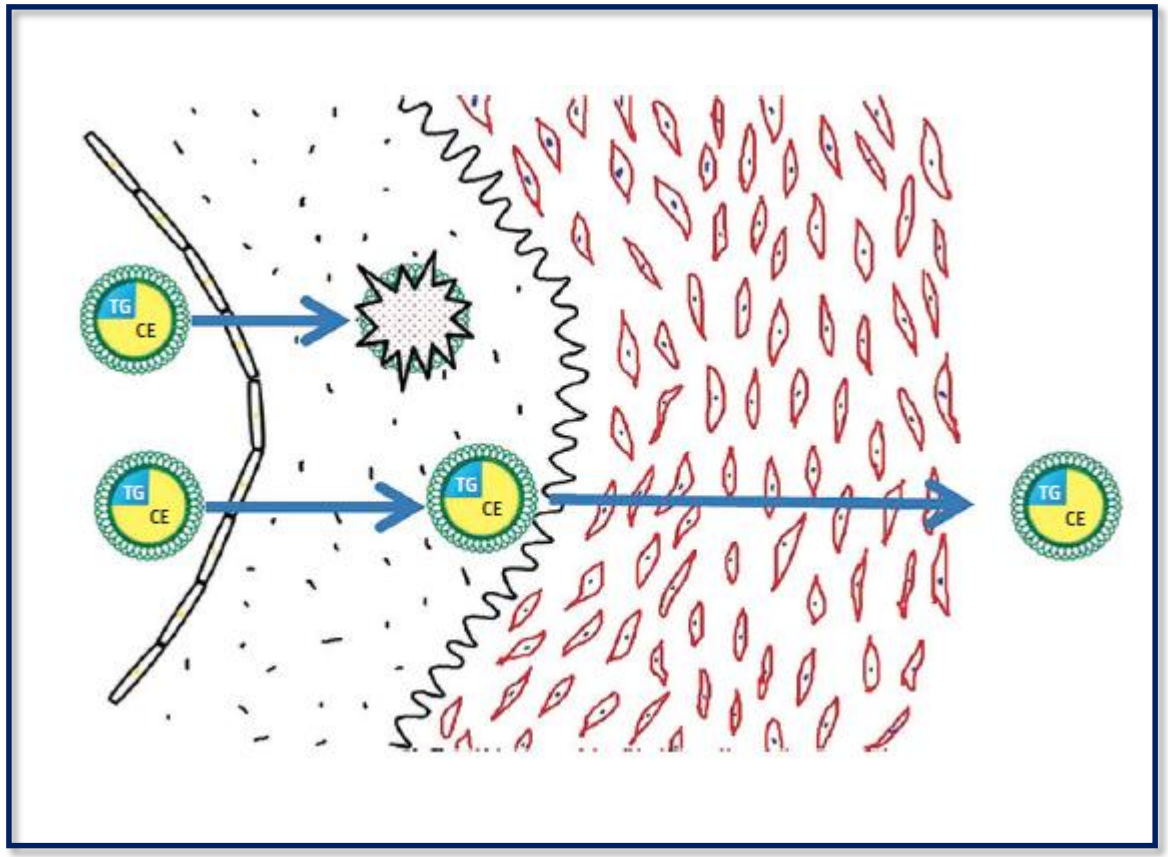
apoB-containing lipoproteins



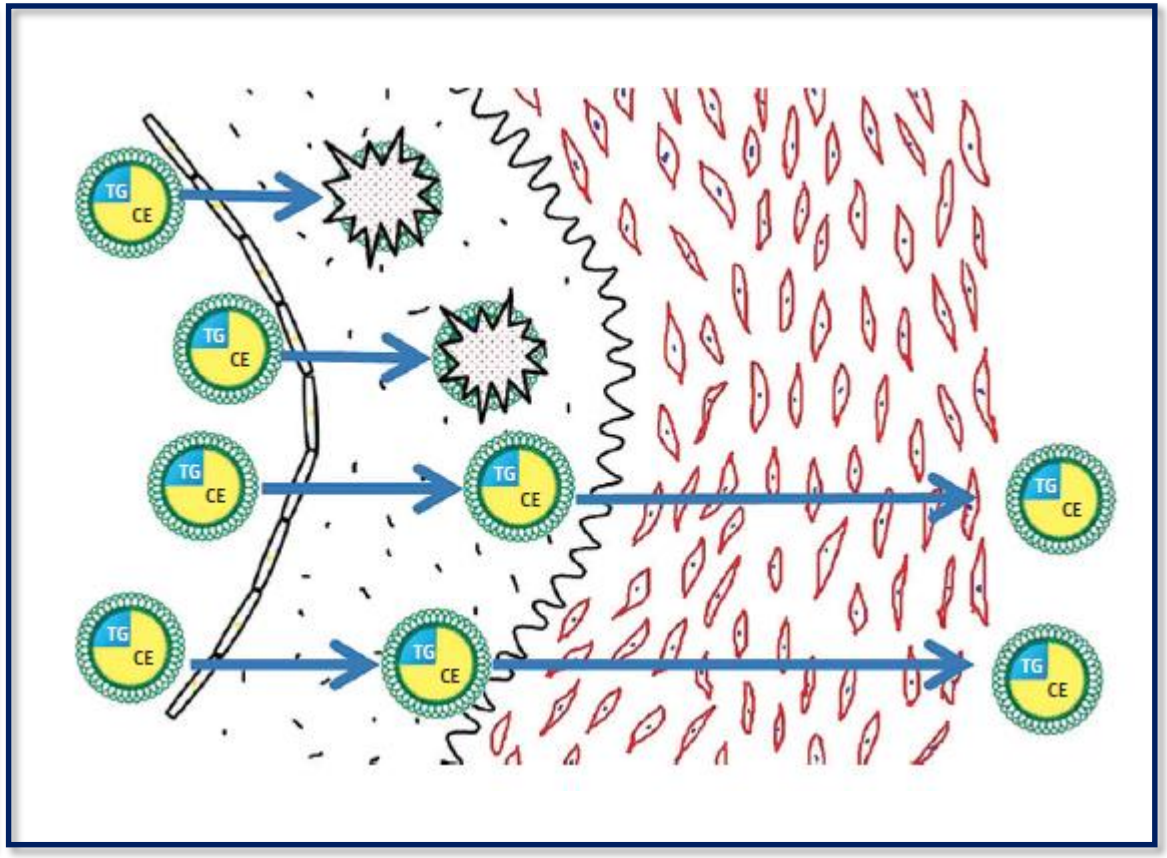
Sniderman AD,.... Catapano AL, Ference BA. JAMA Cardiol. doi:10.1001/jamacardio.2019.3780.

Retention of apoB-containing lipoproteins

Lower plasma LDL / apoB concentration

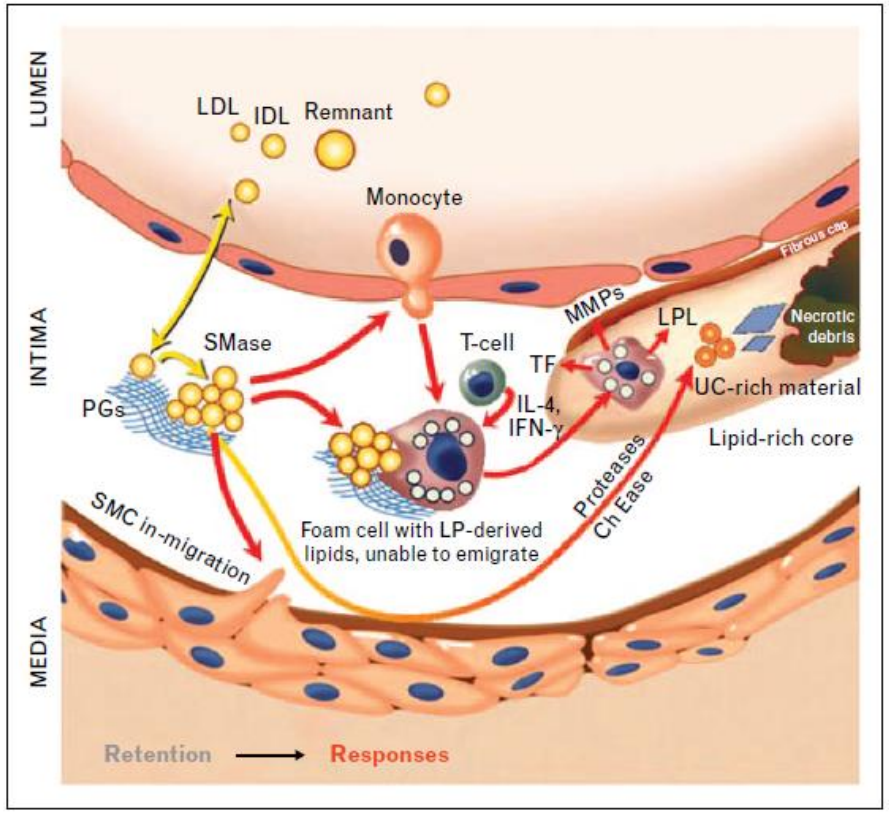


Higher plasma LDL / apoB concentration

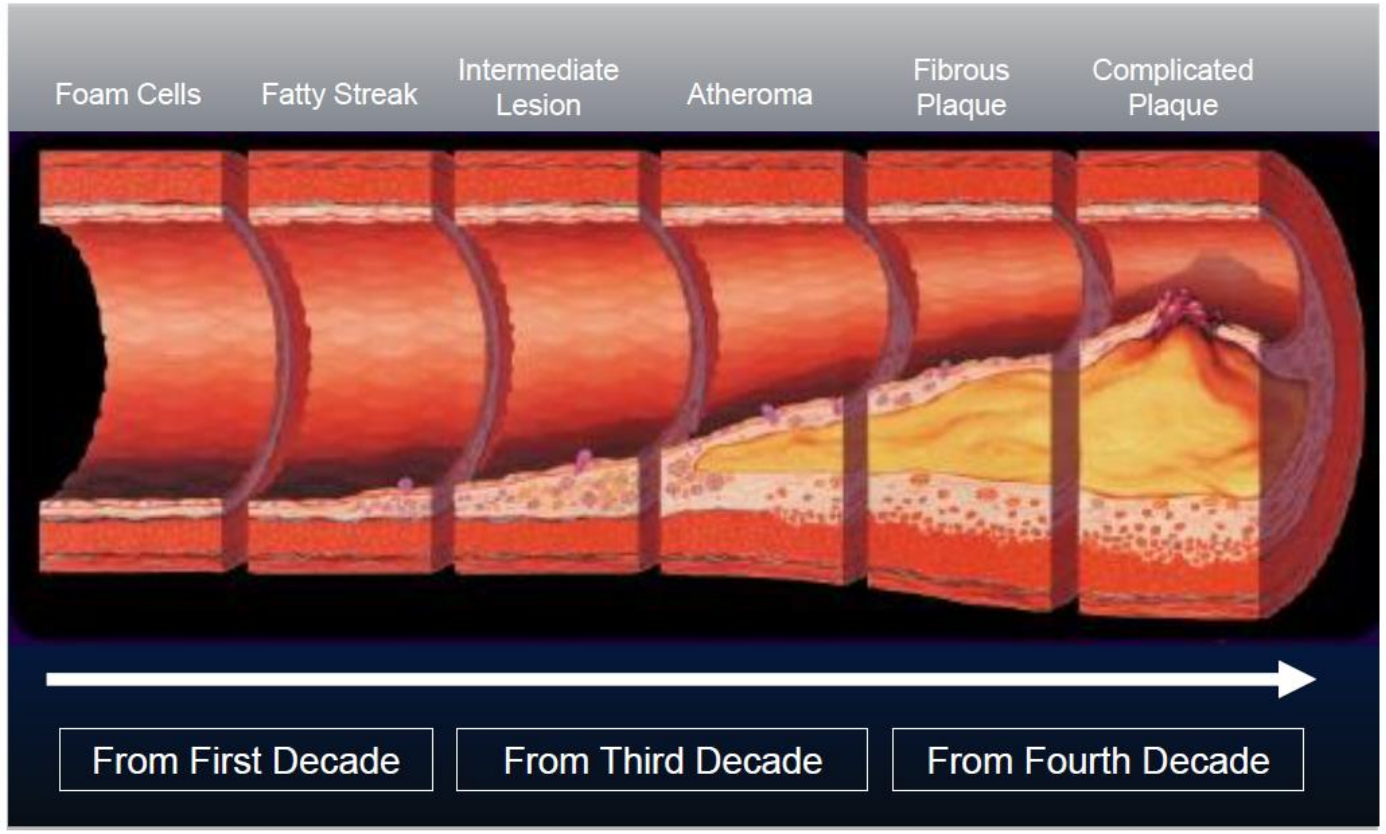


Sniderman AD,.... Catapano AL, Ference BA. JAMA Cardiol. doi:10.1001/jamacardio.2019.3780.

Pathophysiology of Atherosclerosis



ASCVD: Response-to-retention



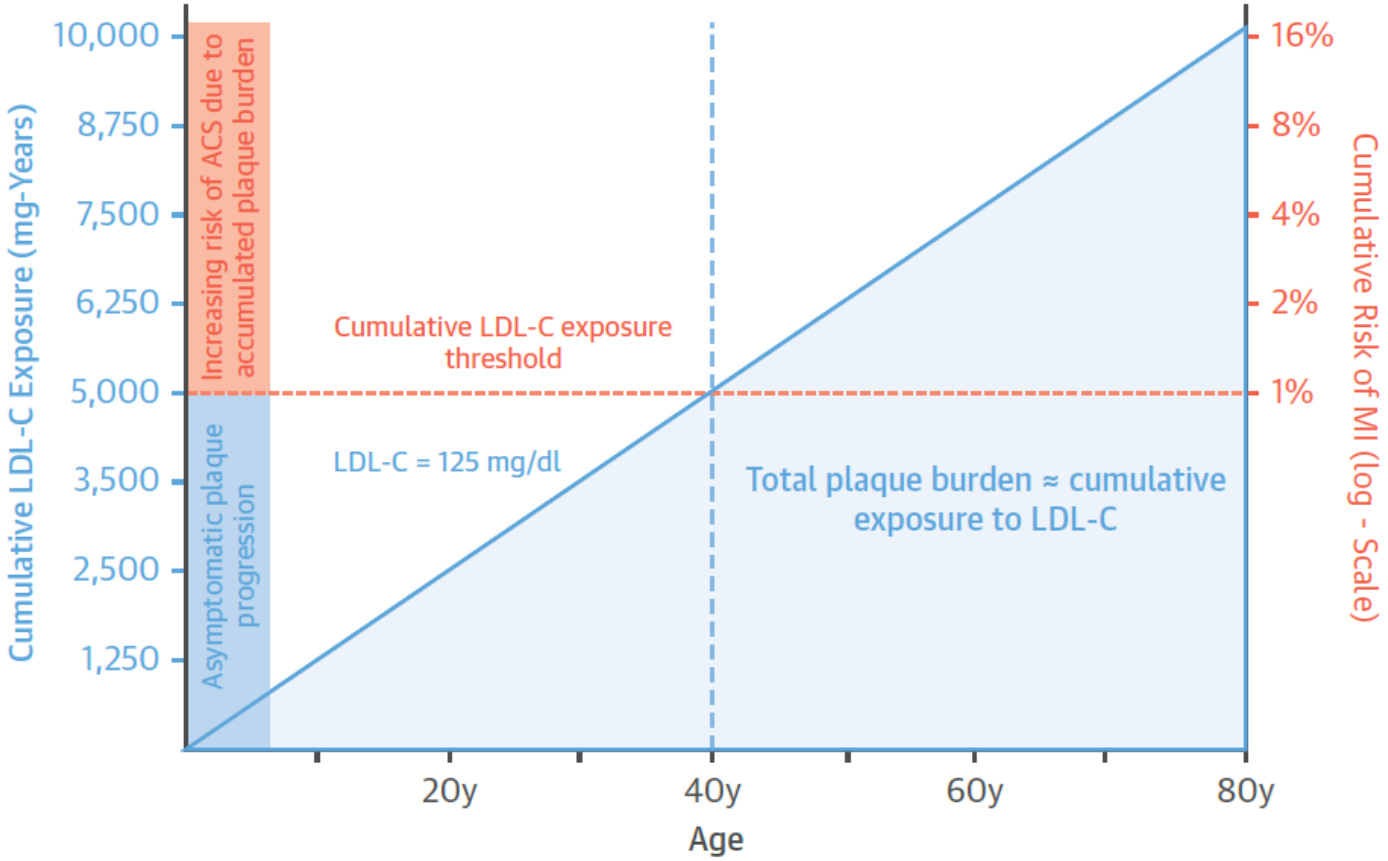
Coronary atherosclerosis progression

Boren J, Williams KJ. Curr Opin Lipidol 2016, 27:473–483.

Adapted from Pepine CJ. *Am J Cardiol.* 1998;82(suppl 104).

Cumulative exposure hypothesis of ASCVD

FIGURE 1 Effect of Cumulative Exposure to LDL on Plaque Burden and Risk of Cardiovascular Disease



Ference BA, et al. J Am Coll Cardiol 2018;72:1141–56

Cumulative exposure hypothesis of ASCVD

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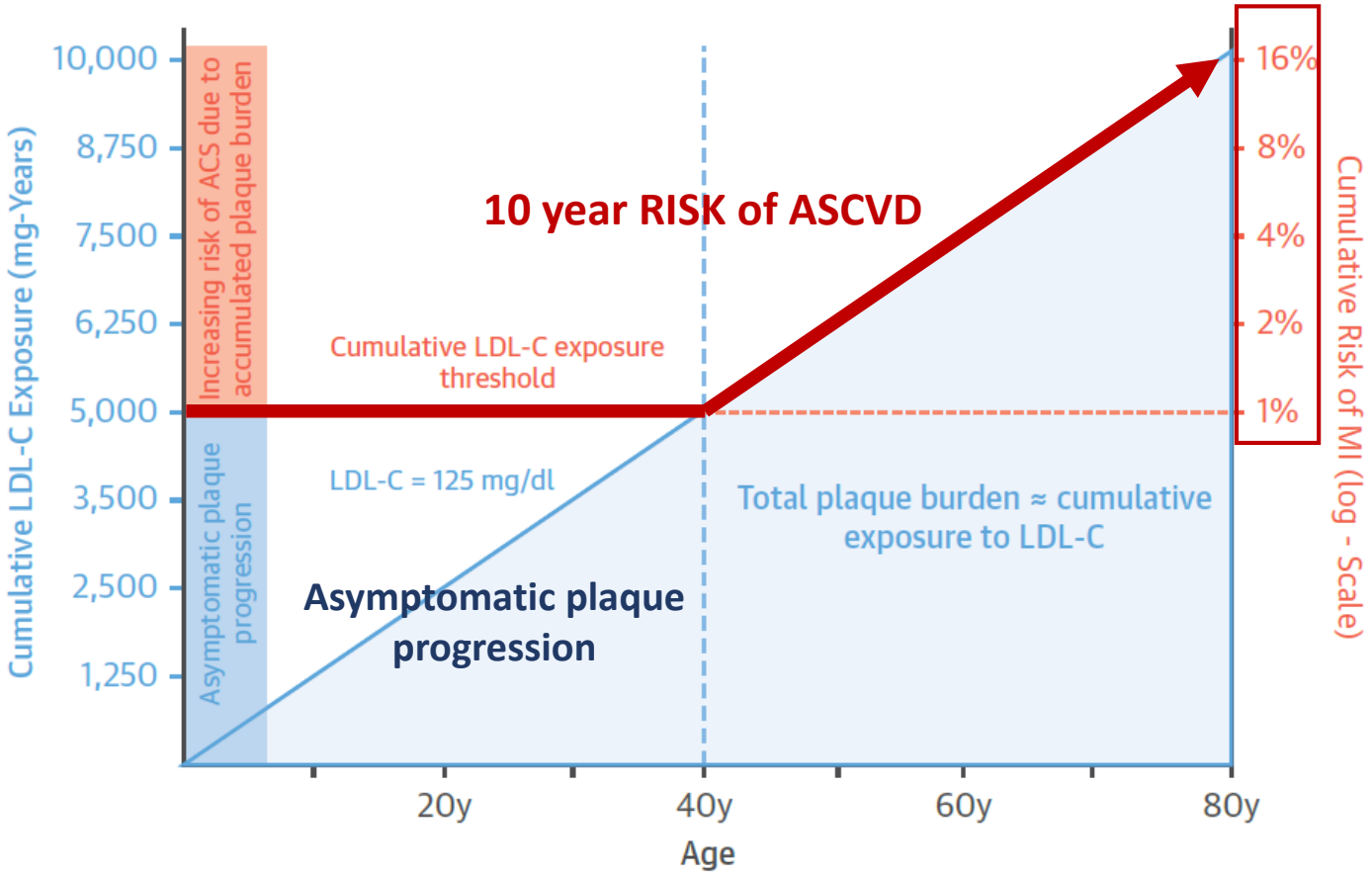
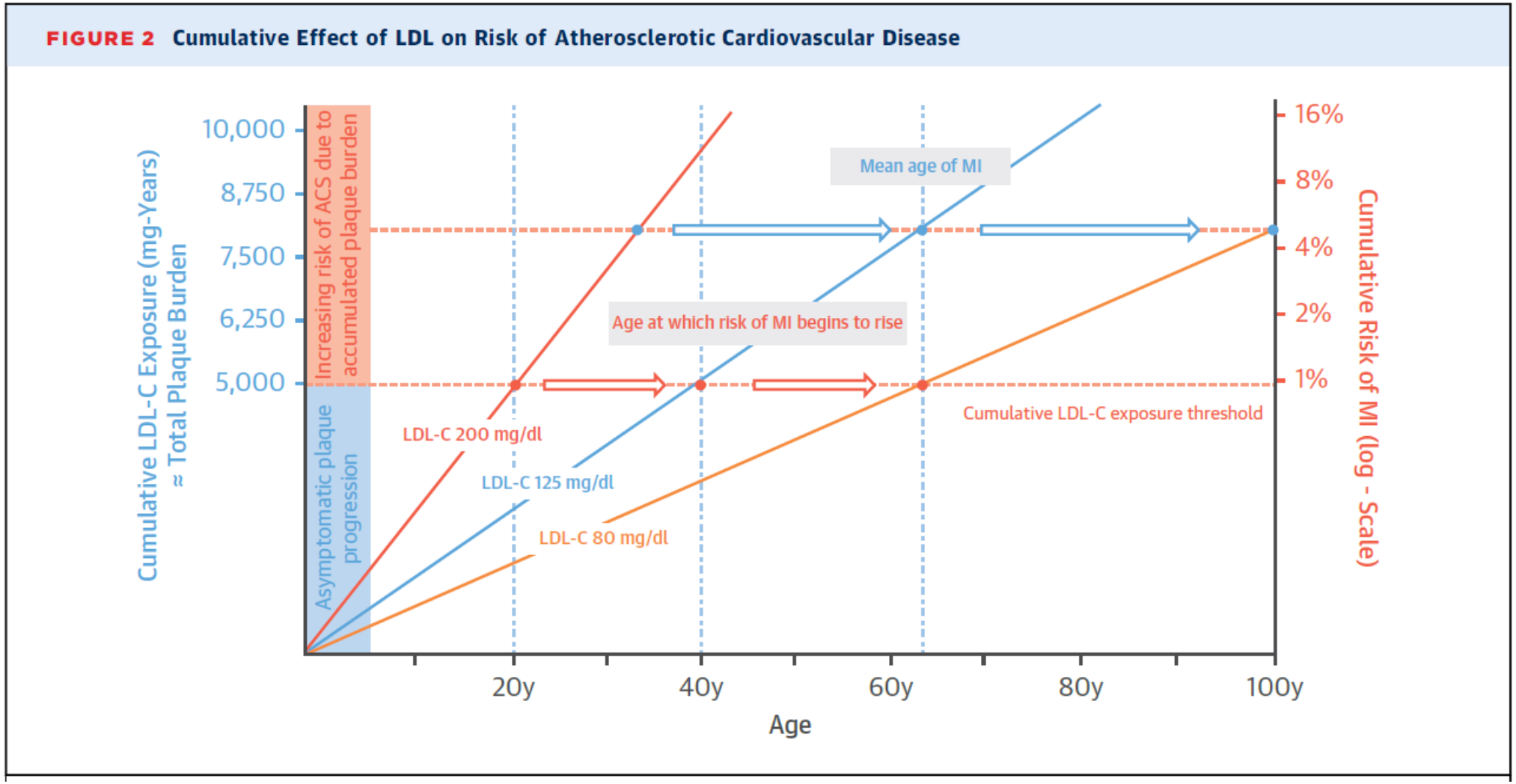


Ference BA, et al. J Am Coll Cardiol 2018;72:1141–56

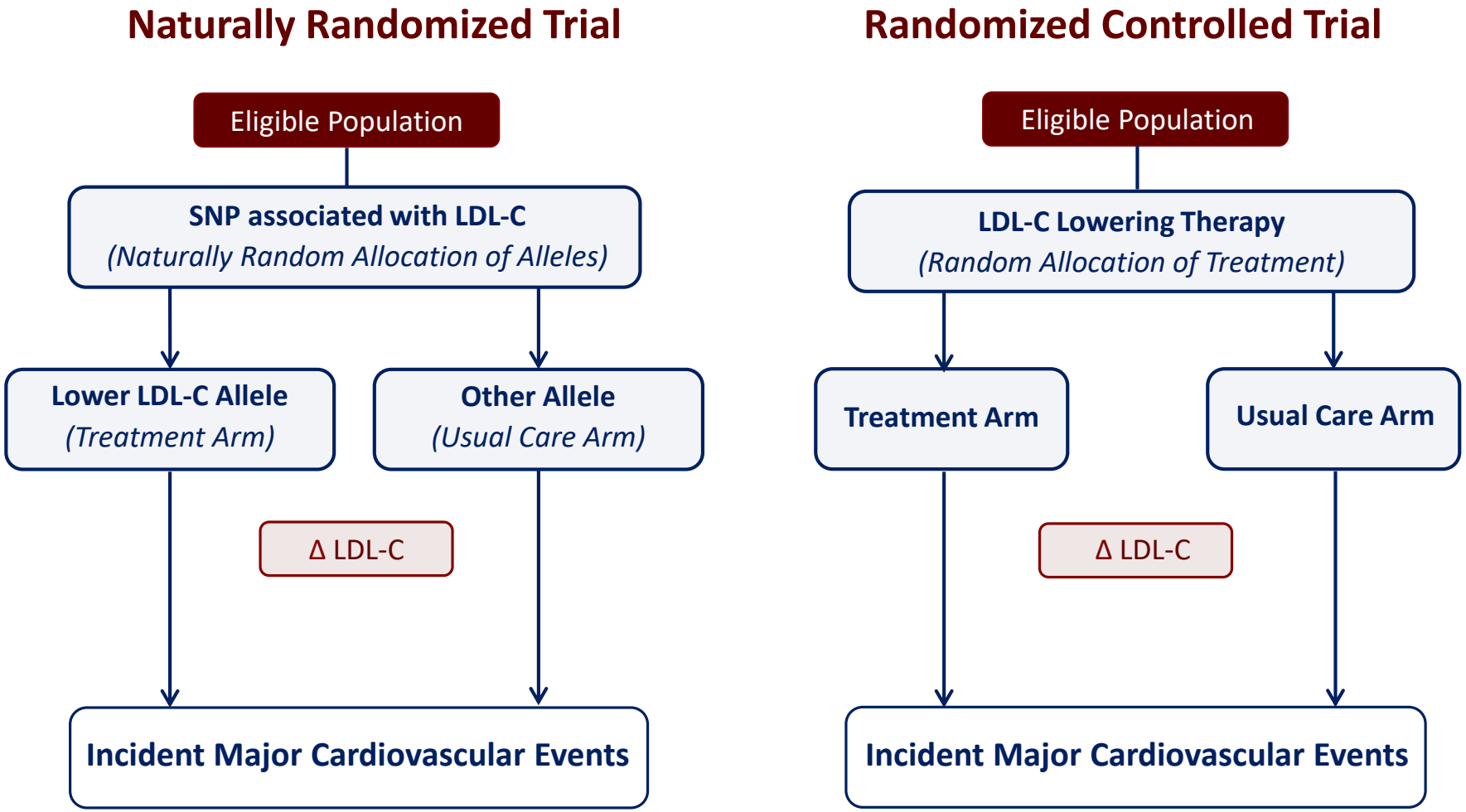
Modifying disease course by slowing progression atherosclerosis



Ference BA, et al. J Am Coll Cardiol 2018;72:1141–56

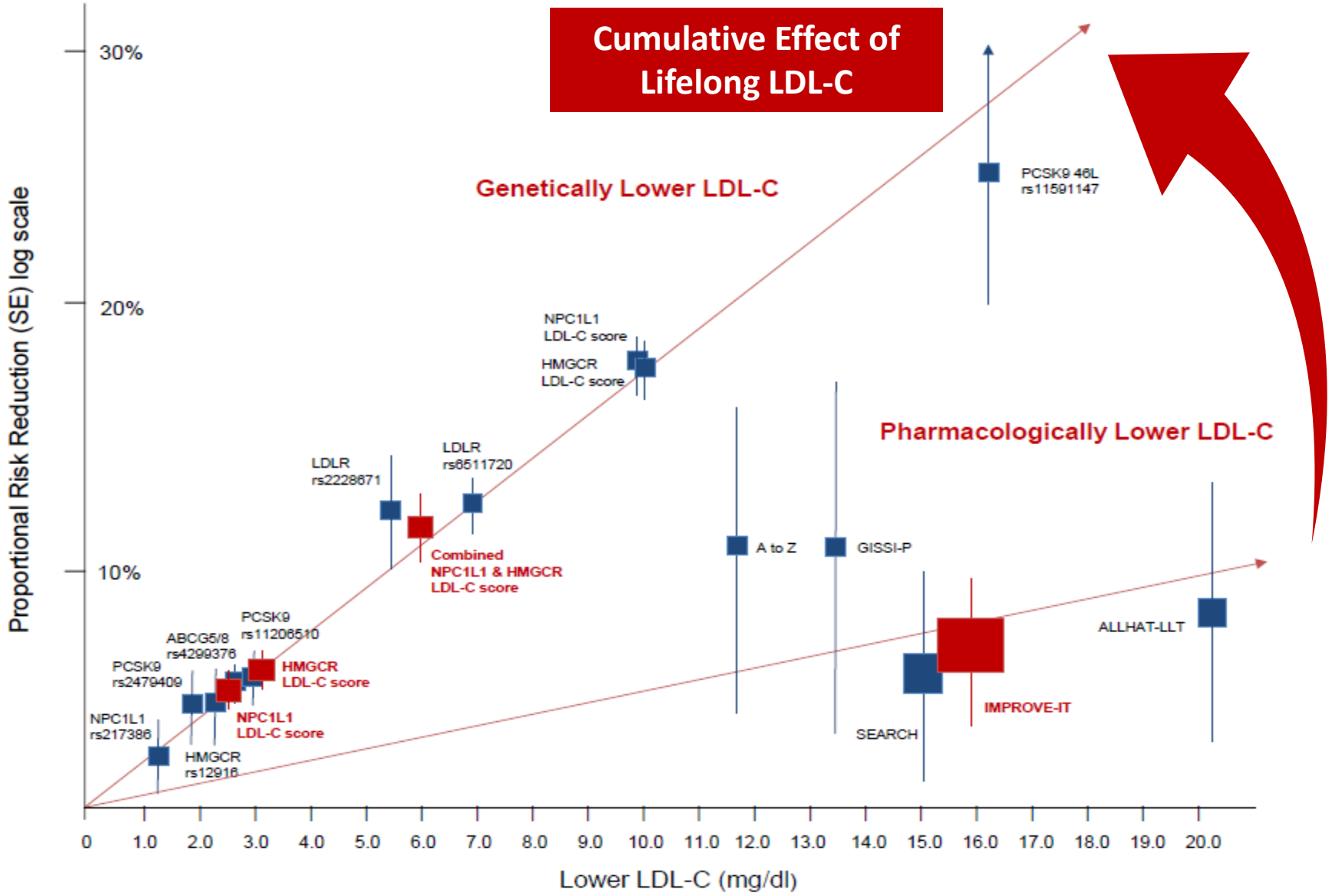
Figure Courtesy of Dr Eugene Braunwald

Mendelian Randomization: nature's randomized trial



Ference BA, et al. J Am Coll Cardiol 2018;72:1141–56

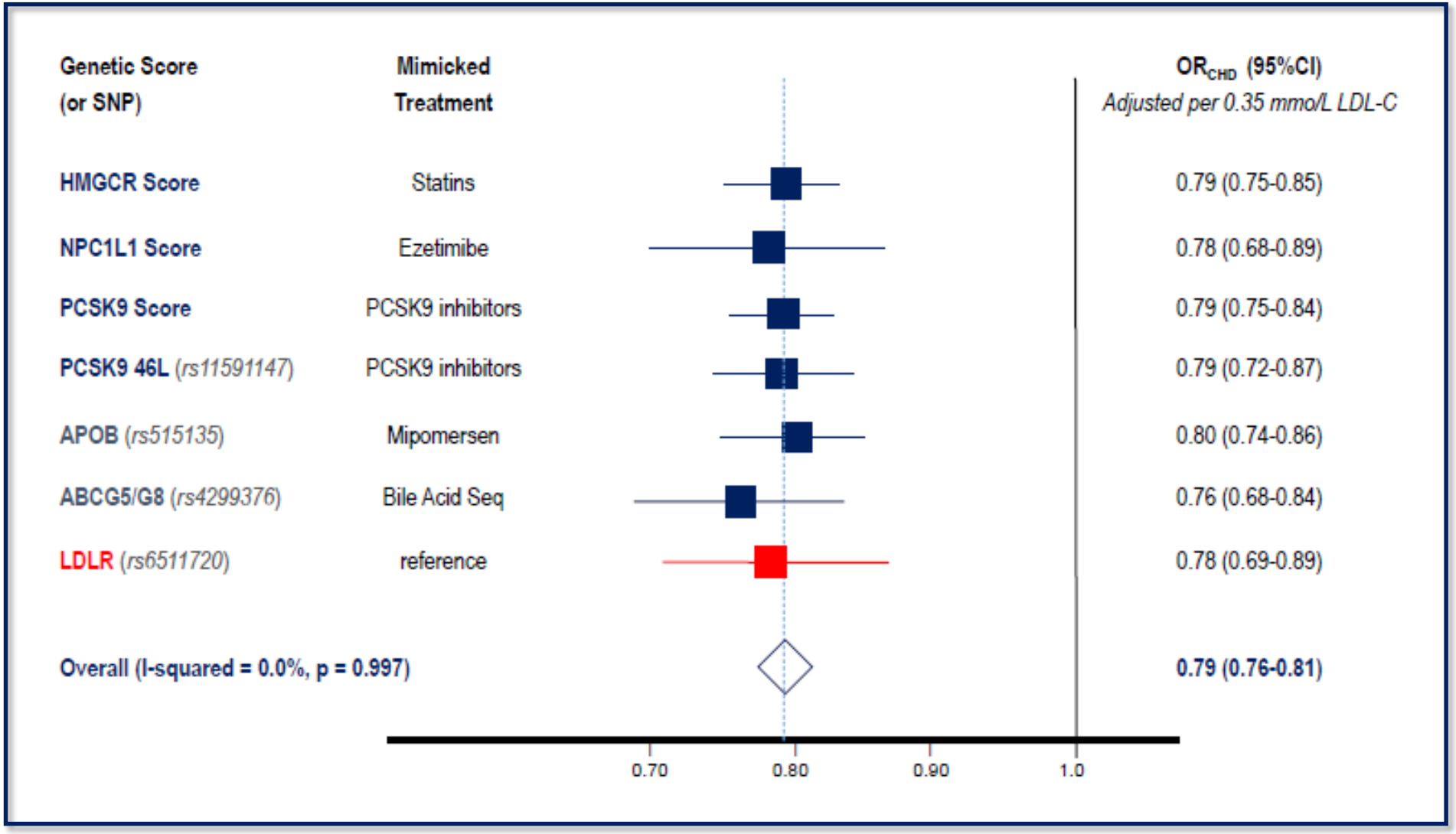
LDL has BOTH a causal and a cumulative effect on CHD risk



Ference, BA et al. J Am Coll Cardiol 2015;65:1552–61.

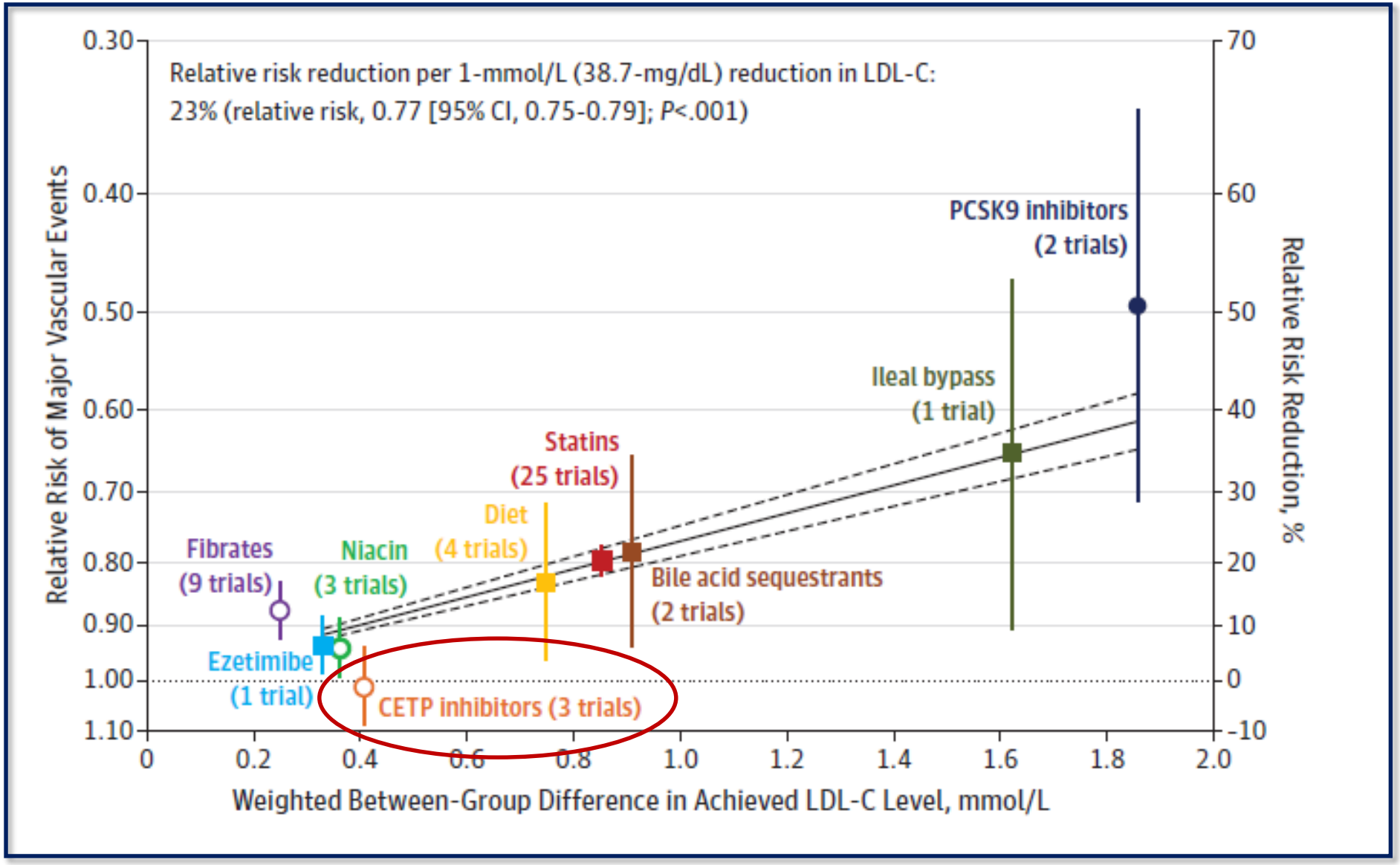
Ference, BA et al. J Am Coll Cardiol 2012;60:2631-9.

Naturally randomized trials of various methods to lower LDL-C



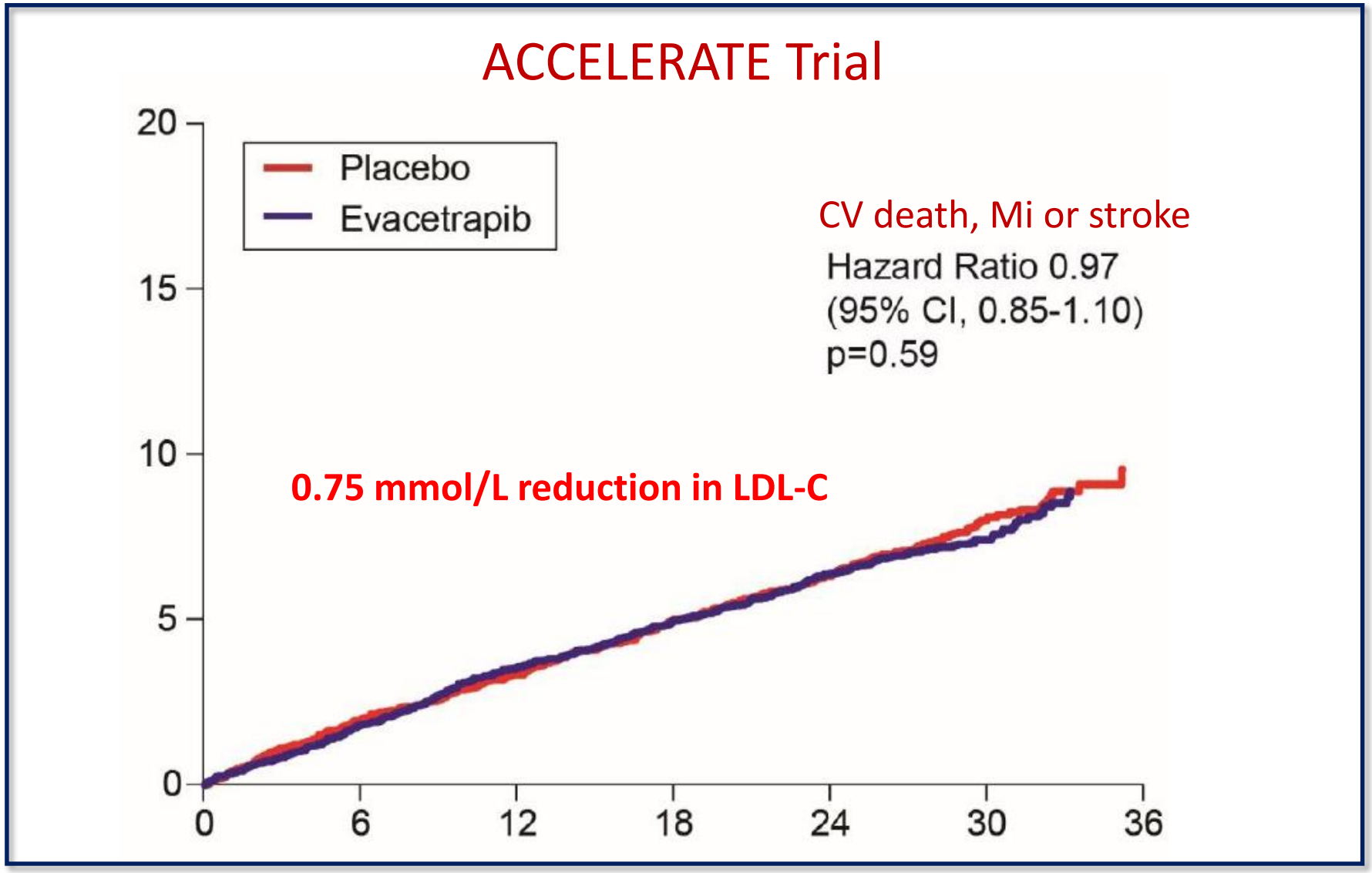
Ference BA, et al. EAS Consensus Statement on LDL Causality. Eur Heart J 2017; doi: 10.1093/eurheartj/ehx144

Meta-Analysis of Various Methods to Lower LDL-C



Silverman MG, Ference BA, et al. JAMA 2016;316:1289-1297.

Does mechanism of lowering LDL-C matter?

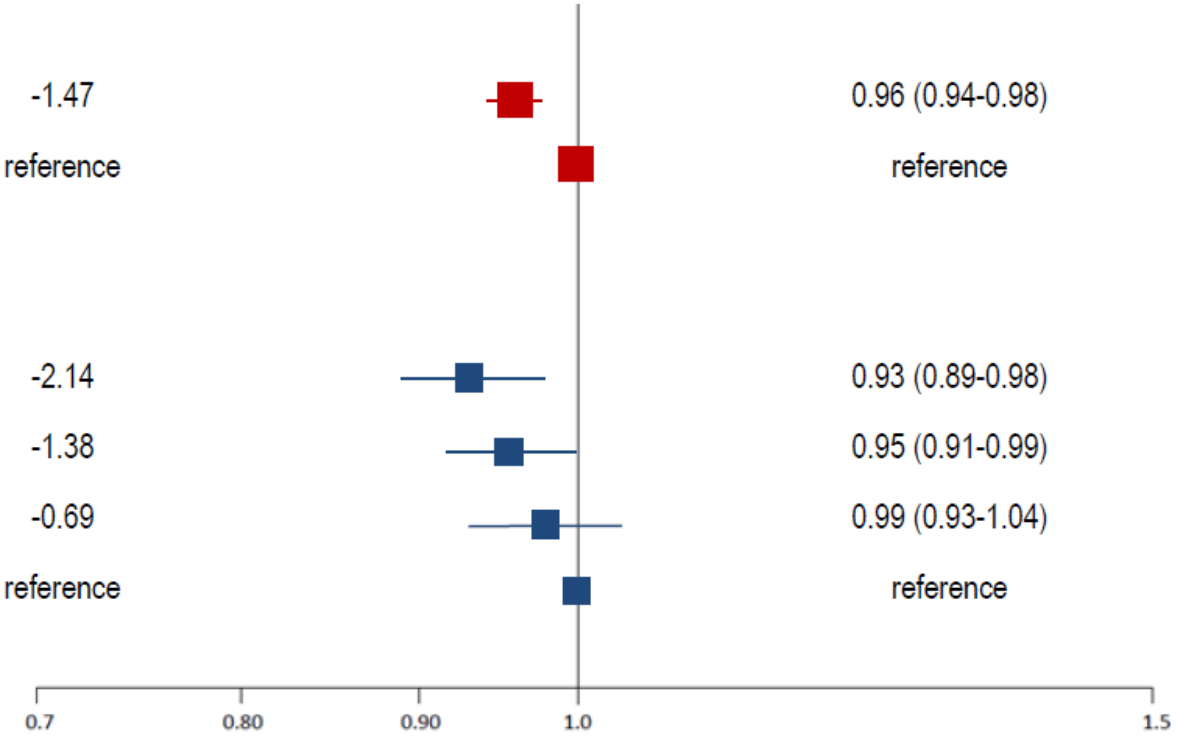


Lincoff AM, et al. N Engl J Med. 2017; 376:1933-1942.

CETP genetically validated target

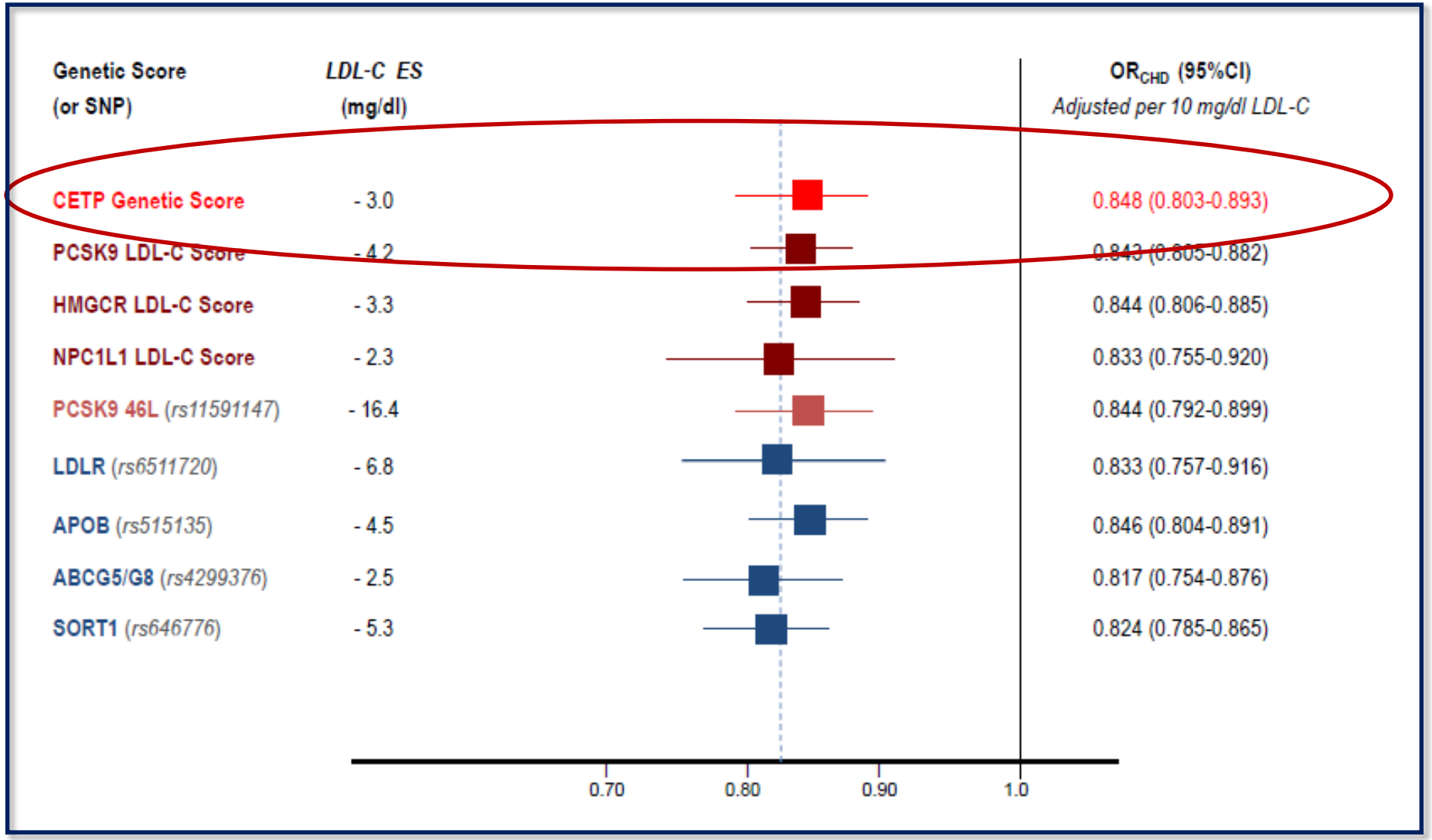
dose response effect of CETP inhibition on CHD risk

Analysis	Δ HDL-C (95% CI)	Δ LDL-C (95% CI)	Δ apoB (95% CI)	OR_{MVE} (95%CI)
Primary Analysis				
CETP score ≥ median	4.62	-2.15	-1.47	0.96 (0.94-0.98)
CETP score < median	Reference	reference	reference	reference
Dose Response				
CETP score quartile 4	7.12	-3.29	-2.14	0.93 (0.89-0.98)
CETP score quartile 3	4.98	-2.32	-1.38	0.95 (0.91-0.99)
CETP score quartile 2	2.37	-0.95	-0.69	0.99 (0.93-1.04)
CETP score quartile 1	reference	reference	reference	reference



Ference BA, et al. JAMA. 2017; 318(10):947-956

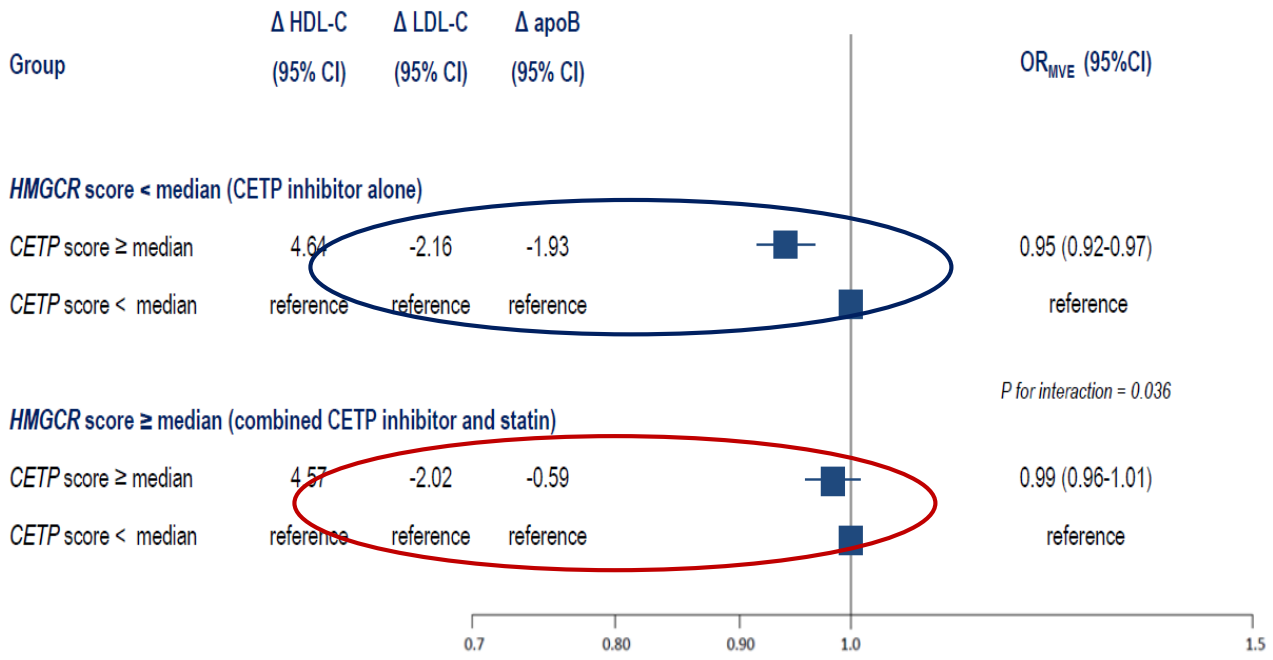
CETP, PCSK9, HMGCR & NPC1L1 genetic scores



Ference BA, et al. JAMA. 2017; 318(10):947-956

Causal effect of LDL determined by LDL-C or LDL-P (apoB)?

Combined effect of CETP and HMGCR inhibition



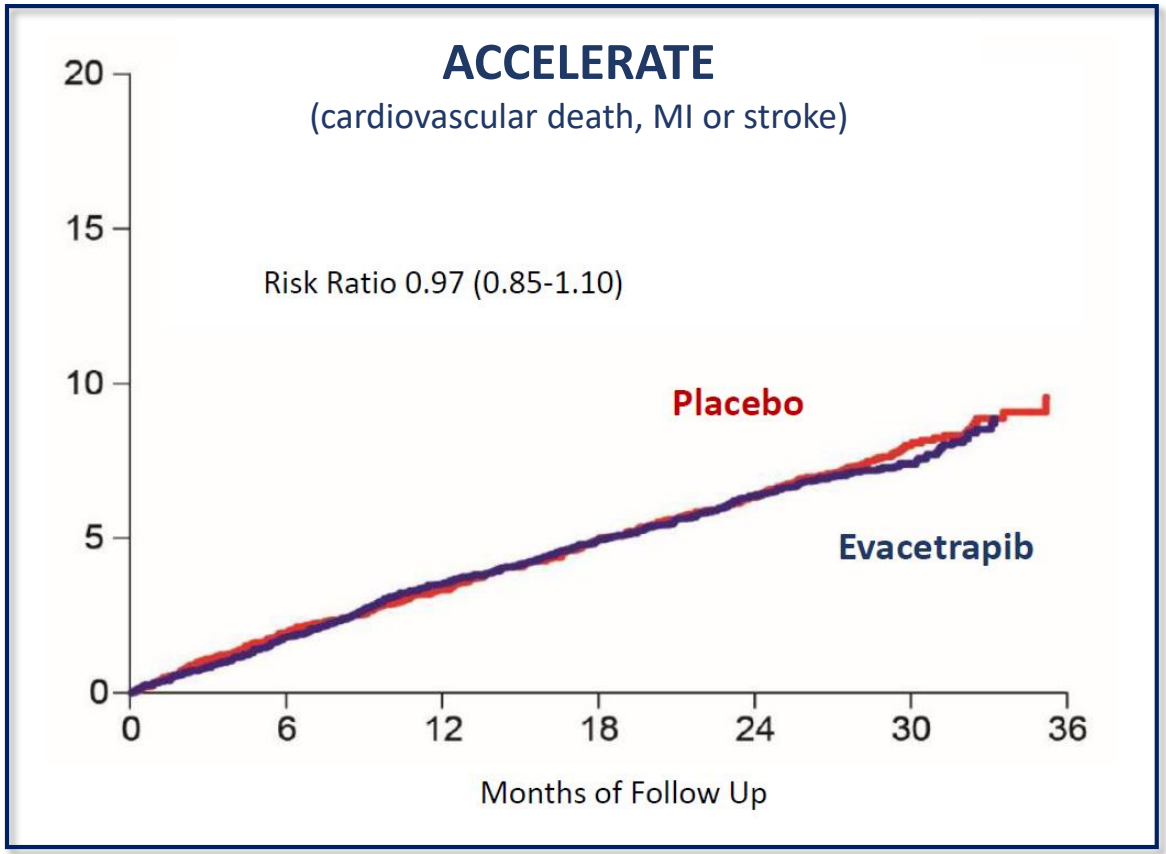
Combined CETP inhibitor and statin

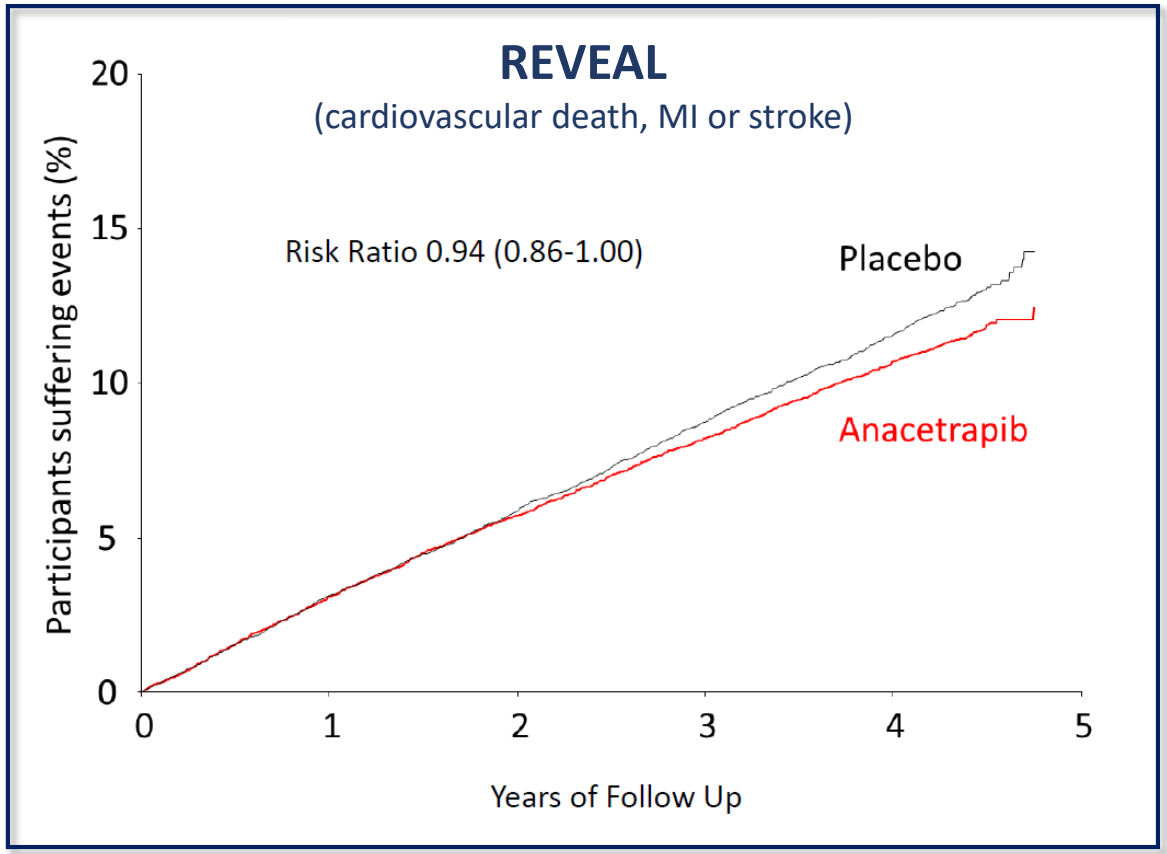
CETP inhibitor	Δ LDL-C	Δ APOB
JAMA 2011 RCT		
Evacetrapib monotherapy	23%	17%
Evacetrapib + statin	22%	11%
TULIP Trial		
TA-8995 monotherapy	46%	35%
TA-8995 plus statin	45%	17%

Ference BA, et al. JAMA. 2017; 318(10):947-956

Nicholls SJ et al. JAMA. 2011;306:2099 Hovingh GK, et al. Lancet 2015; 386: 452

Benefit of CETP inhibition proportional absolute apoB reduction





Biomarker	Change mg/dL (%)	Expected RRR	Observed RRR
Beta-Quant	-29 (-37%)	10.5%	3.0%
apoB	-13 (-15%)	3.1%	3.0%

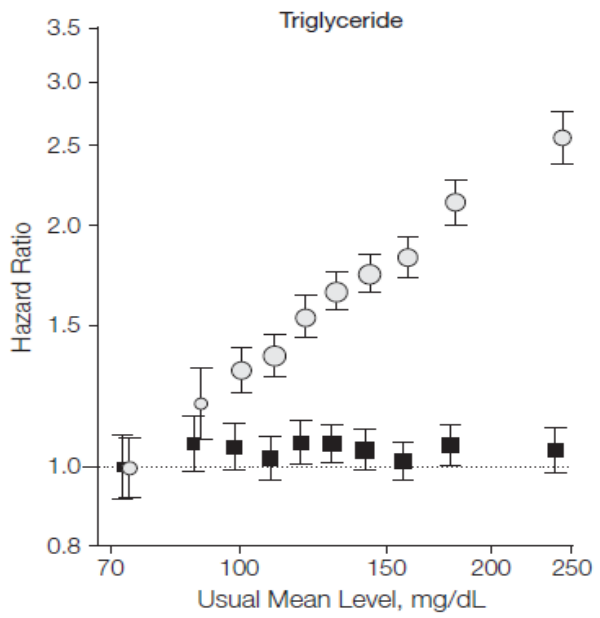
Biomarker	Change mg/dL (%)	Expected RRR	Observed RRR
LDL-C (direct)	-24 (-41%)	15.5%	6.3%
apoB	-12 (-18%)	6.5%	6.3%

Lincoff AM, et al. N Engl J Med 2017;376:1933-42.

HPS3/TIMI55–REVEAL Collaborative Group. N Engl J Med. 2017;377(13):1217-1227.

Triglycerides and risk of CHD

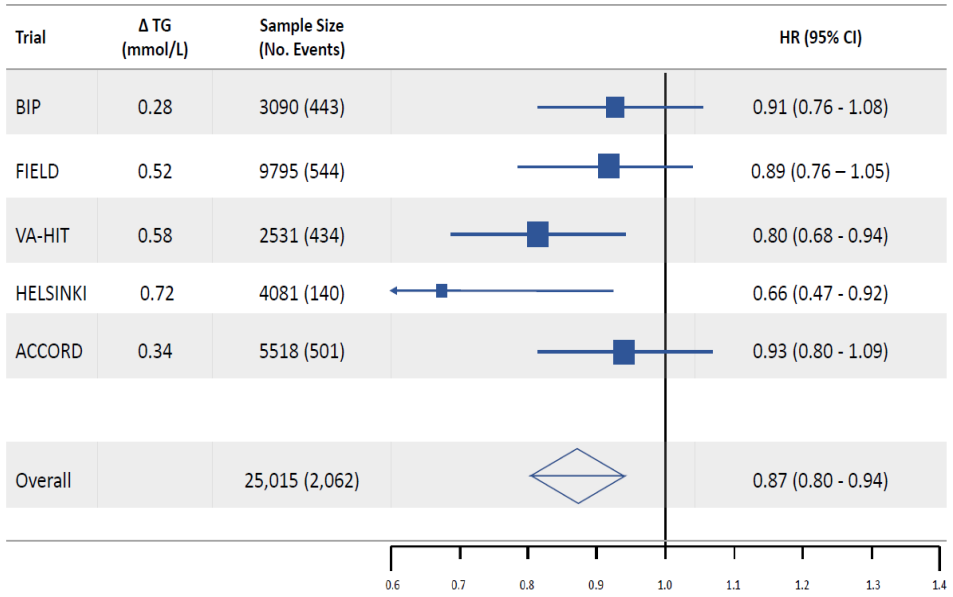
Observational epidemiology



Mendelian Randomization

Outcome	Predictor	Covariate	Beta	SE	P
β_{CAD}	$\beta_{LDL\text{-}C}$	-	0.41	0.039	4×10^{-20}
β_{CAD}	$\beta_{LDL\text{-}C}$	$\beta_{HDL\text{-}C}$	0.38	0.039	9×10^{-19}
β_{CAD}	$\beta_{LDL\text{-}C}$	$\beta_{TRIGLYCERIDES}$	0.40	0.034	1×10^{-23}
β_{CAD}	$\beta_{LDL\text{-}C}$	$\beta_{HDL\text{-}C}$, $\beta_{TRIGLYCERIDES}$	0.38	0.034	2×10^{-22}
β_{CAD}	$\beta_{HDL\text{-}C}$	-	−0.18	0.052	0.0006
β_{CAD}	$\beta_{HDL\text{-}C}$	$\beta_{LDL\text{-}C}$	−0.12	0.041	0.005
β_{CAD}	$\beta_{HDL\text{-}C}$	$\beta_{TRIGLYCERIDES}$	−0.09	0.048	0.057
β_{CAD}	$\beta_{HDL\text{-}C}$	$\beta_{LDL\text{-}C}$, $\beta_{TRIGLYCERIDES}$	−0.04	0.037	0.35
β_{CAD}	$\beta_{TRIGLYCERIDES}$	-	0.44	0.074	2×10^{-8}
β_{CAD}	$\beta_{TRIGLYCERIDES}$	$\beta_{LDL\text{-}C}$	0.42	0.057	5×10^{-12}
β_{CAD}	$\beta_{TRIGLYCERIDES}$	$\beta_{HDL\text{-}C}$	0.36	0.074	3×10^{-6}
β_{CAD}	$\beta_{TRIGLYCERIDES}$	$\beta_{LDL\text{-}C}$, $\beta_{HDL\text{-}C}$	0.36	0.057	1×10^{-9}

Fibrate randomized trials

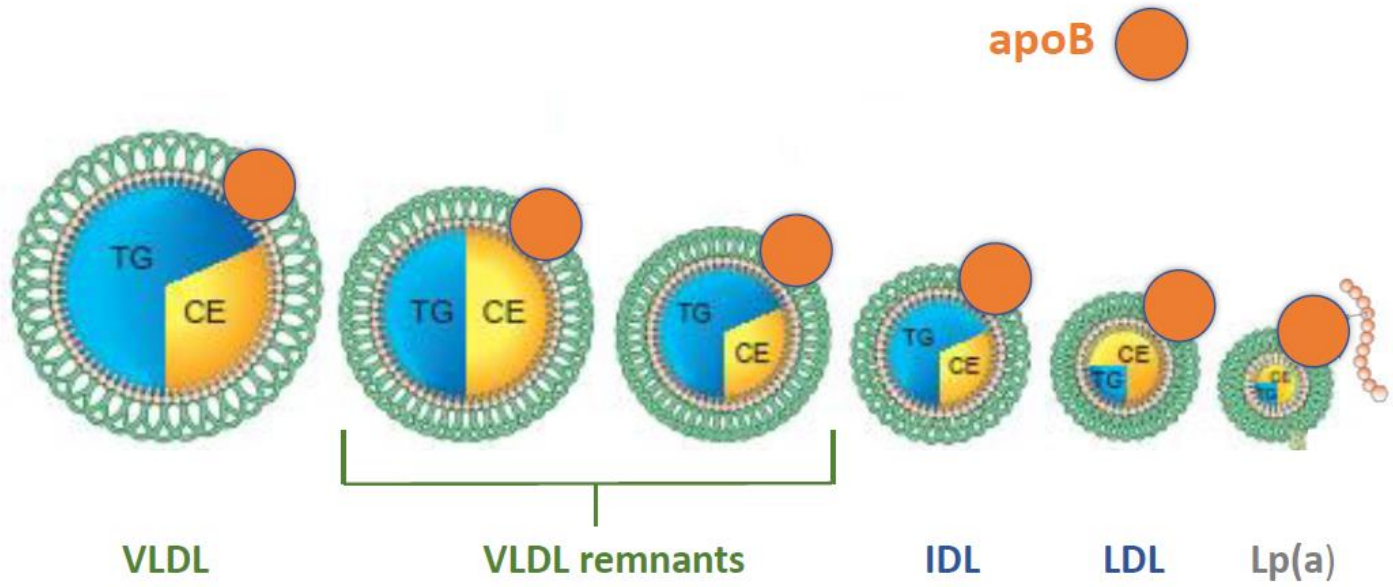


Emerging Risk Factors Collaboration. JAMA. 2009;302(18):1993-2000.
Varbo A, etal. JACC 2013;61:427–36. Do R et al. Nat Genet. 2013;45:1345–1352.

BIP: Circulation. 2000;102:21-27; Field: Lancet 2005; 366: 1849–61; VA-HIT: N Engl J Med 1999;341:410-8; Helsinki: N Engl J Med 1987;317:1237-45; ACCORD: N Engl J Med 2010;362:1563-74.

Directly comparing effect of lowering triglycerides and LDL-C on CHD

- Triglyceride-rich VLDL and their remnants particles, and LDL particles each have one apoB100
- Therefore, the effect of lowering triglycerides on the risk of cardiovascular events can be directly compared with the effect of lowering LDL-C by comparing their effects per unit change in apoB

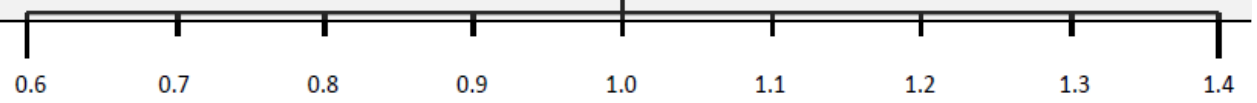


Ference BA, et al. JAMA 2019;321(4):1-11

Effect of *LPL* and *LDLR* scores on lipids & CHD per unit change apoB

Effects on lipids and CHD for a common 10 mg/dL decrease in apoB-containing lipoproteins

Genetic Score	Δ triglycerides, mg/dL (95%CI)	Δ LDL-C, mg/dL (95%CI)	OR_{CHD} (95% CI) per 10 mg/dl lower apoB
LPL score	**-69.9** (-68.3, -71.6) **p = 7.1x10 $^{-1363}$**	**0.7** (0.0, 1.4) p = 0.039	0.771 (0.741 - 0.802) p = 3.9x10 $^{-38}$
LDLR Score	**-1.9** (-0.1, -3.9) p = 0.036	**-14.2** (-13.6, -14.8) **p = 1.4x10 $^{-465}$**	0.773 (0.747 - 0.801) p = 1.1x10 $^{-46}$



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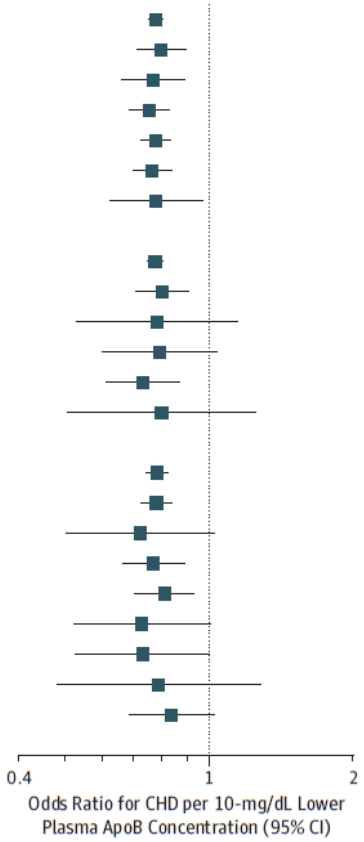
Effect variants in targets of lipid lowering therapies on risk of CHD

Per 10 mg/dl lower apoB

Figure 2. Association of Genetic Variants and Genetics Scores With Triglycerides, Low-Density Lipoprotein Cholesterol (LDL-C), and Risk of Coronary Heart Disease (CHD) per 10-mg/dL Lower Concentration of Apolipoprotein B (ApoB)-Containing Lipoproteins

Gene	Genetic Variant	Functional Consequence	Therapy	Δ Triglycerides (95% CI)	Δ Low-Density Lipoprotein Cholesterol (95% CI)	Odds Ratio (95% CI)	*P* Value
LDL-C lowering through LDL receptor pathway							
LDLR	3 Variants	Genetic score	Therapeutic target	-1.9 (-3.9 to -0.1)	-14.2 (-14.8 to -13.6)	0.773 (0.746 to 0.801)	1.1×10^{-46}
HMGCR	rs3846662	Intron	Statin	-2.4 (-5.9 to 1.0)	-15.6 (-16.8 to -14.3)	0.795 (0.706 to 0.894)	1.3×10^{-4}
NPC1L1	rs217386	Intron	Ezetimibe	-7.6 (-14.8 to -0.5)	-14.6 (-17.6 to -11.6)	0.762 (0.654 to 0.887)	14.5×10^{-4}
PCSK9	rs11206510	Intergenic	PCSK9 inhibitor	-4.2 (-7.1 to -1.3)	-10.9 (-12.0 to -9.8)	0.748 (0.679 to 0.823)	3.1×10^{-9}
PCSK9 46L	rs11591147	Arg46Leu	PCSK9 inhibitor	-0.5 (-2.7 to 1.7)	-18.0 (-18.8 to -17.2)	0.774 (0.721 to 0.832)	2.6×10^{-12}
ABCG5/G8	rs4245791	Intron	Bile resin	-9.0 (-11.8 to -6.2)	-12.6 (-13.7 to -11.6)	0.761 (0.693 to 0.834)	6.7×10^{-9}
CETP	rs5880	Ala390Pro	CETP inhibitor	-24.4 (-32.6 to -16.2)	-4.1 (-7.3 to -0.8)	0.774 (0.618 to 0.967)	.03
Triglyceride lowering through LPL pathway							
LPL	5 Variants	Genetic score	Therapeutic target	-69.9 (-71.6 to -68.1)	0.7 (0.0 to 1.4)	0.771 (0.741 to 0.802)	3.9×10^{-38}
APOA5	rs3135506	Ser19Trp	LPL enhancer	-70.7 (-73.9 to -67.5)	-6.0 (-7.4 to -4.6)	0.798 (0.704 to 0.904)	4.1×10^{-4}
APOC3	rs138326449	Essential_Splice_Site	APOC3 inhibitor	-92.3 (-103.8 to -80.3)	-5.7 (-9.7 to -1.8)	0.778 (0.527 to 1.149)	.21
ANGPTL3	rs72649576	Intron	ANGPTL3 inhibitor	-30.9 (-69.7 to 7.8)	-8.9 (-20.3 to 2.4)	0.788 (0.598 to 1.040)	.09
ANGPTL4	rs116843064	Glu40Lys	ANGPTL4 inhibitor	-69.4 (-74.3 to -64.5)	-0.4 (-2.2 to 1.5)	0.726 (0.609 to 0.865)	3.5×10^{-9}
PPARA	rs1042311	PPARA:Ala268Val	Fibrate	-25.0 (-38.7 to -11.3)	-16.4 (-21.5 to -11.3)	0.795 (0.506 to 1.248)	.32
Variants in the *APOB* gene							
APOB	8 Variants	Genetic score	Therapeutic target	-9.7 (-11.0 to -8.3)	-15.6 (-16.1 to -15.1)	0.778 (0.737 to 0.821)	6.2×10^{-20}
APOB	rs515135	Intergenic	Therapeutic target	-6.1 (-8.4 to -3.8)	-15.5 (-16.4 to -14.6)	0.776 (0.722 to 0.833)	3.4×10^{-12}
APOB	rs1801702	Arg4270Thr	Therapeutic target	-3.5 (-11.9 to 4.9)	-18.4 (-21.6 to -15.3)	0.719 (0.503 to 1.028)	.07
APOB	rs5742904	Arg3527Gln	Therapeutic target	8.8 (3.6 to 14.1)	-22.1 (-24.1 to -20.1)	0.765 (0.661 to 0.886)	3.6×10^{-4}
APOB	rs533617	His1923Arg	Therapeutic target	-23.6 (-26.8 to -20.4)	-11.6 (-12.8 to -10.4)	0.806 (0.699 to 0.930)	3.0×10^{-3}
APOB	rs12713843	Arg1128His	Therapeutic target	-18.8 (-28.2 to -9.3)	-20.6 (-24.1 to -17.1)	0.724 (0.522 to 1.004)	.053
APOB	rs41288783	Pro994Leu	Therapeutic target	21.0 (9.1 to 32.9)	-24.3 (-28.8 to -19.8)	0.724 (0.525 to 0.999)	.049
APOB	rs13306194	Arg532Trp	Therapeutic target	-14.1 (-19.9 to -8.4)	-6.6 (-8.7 to -4.4)	0.784 (0.480 to 1.280)	.33
APOB	rs1367117	Thr98Ile	Therapeutic target	-9.8 (-12.2 to -7.4)	-17.4 (-18.4 to -16.5)	0.834 (0.679 to 1.025)	.08



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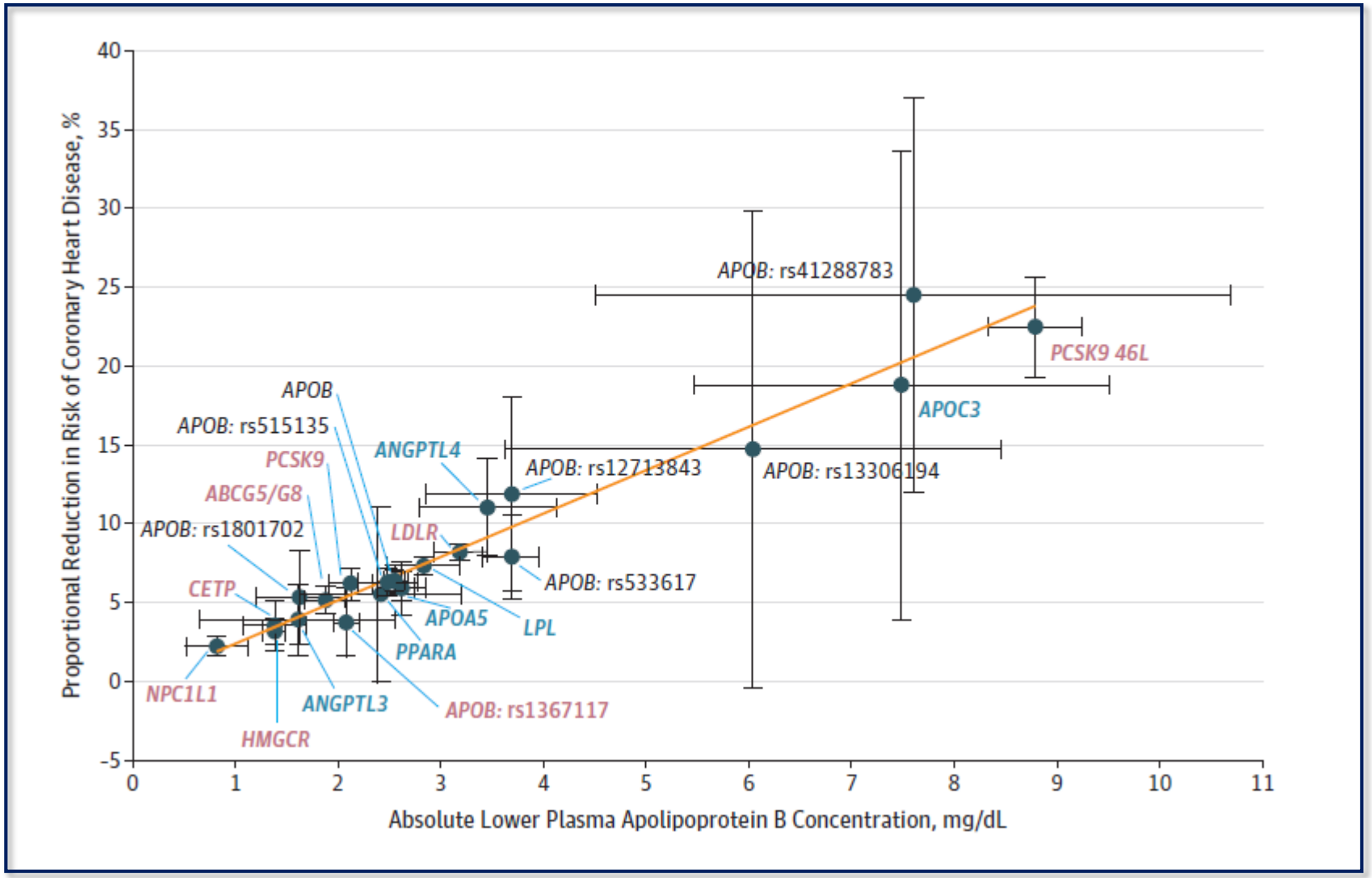
Effect variants in targets of lipid lowering therapies on risk of CHD



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Effect variant associated with LDL, TG or both on risk of CHD

Per 10 mg/dl lower apoB

Table 2. Association of Additional Genetic Scores With Triglycerides, LDL-C, and Risk of CHD per 10-mg/dL Lower Concentration of ApoB-Containing Lipoproteins[a]

Composition of Genetic Score	Δ Triglycerides (95% CI)	Δ LDL-C (95% CI)	Odds Ratio for CHD (95% CI) per 10-mg/dL Lower ApoB
51 Variants associated with triglycerides at $P < 5.0\times10^{-8}$, but not LDL-C ($P > .001$)	−43.1 (−44.5 to −41.7)	−2.1 (−2.6 to −1.6)	0.762 (0.724 to 0.803)
59 Variants associated with LDL-C at $P < 5.0\times10^{-8}$, but not triglycerides ($P > .001$)	−2.1 (−3.0 to −1.1)	−15.5 (−15.8 to −15.1)	0.774 (0.748 to 0.800)
168 Variants associated with either triglycerides or LDL-C at $P < 5.0\times10^{-8}$	−21.6 (−22.1 to −21.1)	−11.8 (−12.0 to −11.6)	0.770 (0.757 to 0.783)
91 Variants associated with triglycerides at $P < 5.0\times10^{-8}$	−35.3 (−35.9 to −34.6)	−9.3 (−9.6 to −9.1)	0.776 (0.758 to 0.795)
100 Variants associated with LDL-C at $P < 5.0\times10^{-8}$	−17.5 (−18.0 to −17.0)	−13.5 (−13.7 to −13.3)	0.776 (0.762 to 0.791)
23 Variants associated with both triglycerides and LDL-C, both at $P < 5.0\times10^{-8}$, in same direction of effect	−32.3 (−33.0 to −31.5)	−12.0 (−12.3 to −11.7)	0.793 (0.771 to 0.815)
10 Variants associated with both triglycerides and LDL-C, both at $P < 5.0\times10^{-8}$, with opposite directions of effect	17.2 (16.0 to 18.4)	−22.5 (−23.0 to −22.1)	0.798 (0.767 to 0.830)
9 Variants associated with both triglycerides and LDL-C, both at $P < 5.0\times10^{-8}$, with opposite directions of effect (excluding *APOE* variant rs7412)	26.0 (23.7 to 28.3)	−20.3 (−21.2 to −19.4)	0.770 (0.711 to 0.833)

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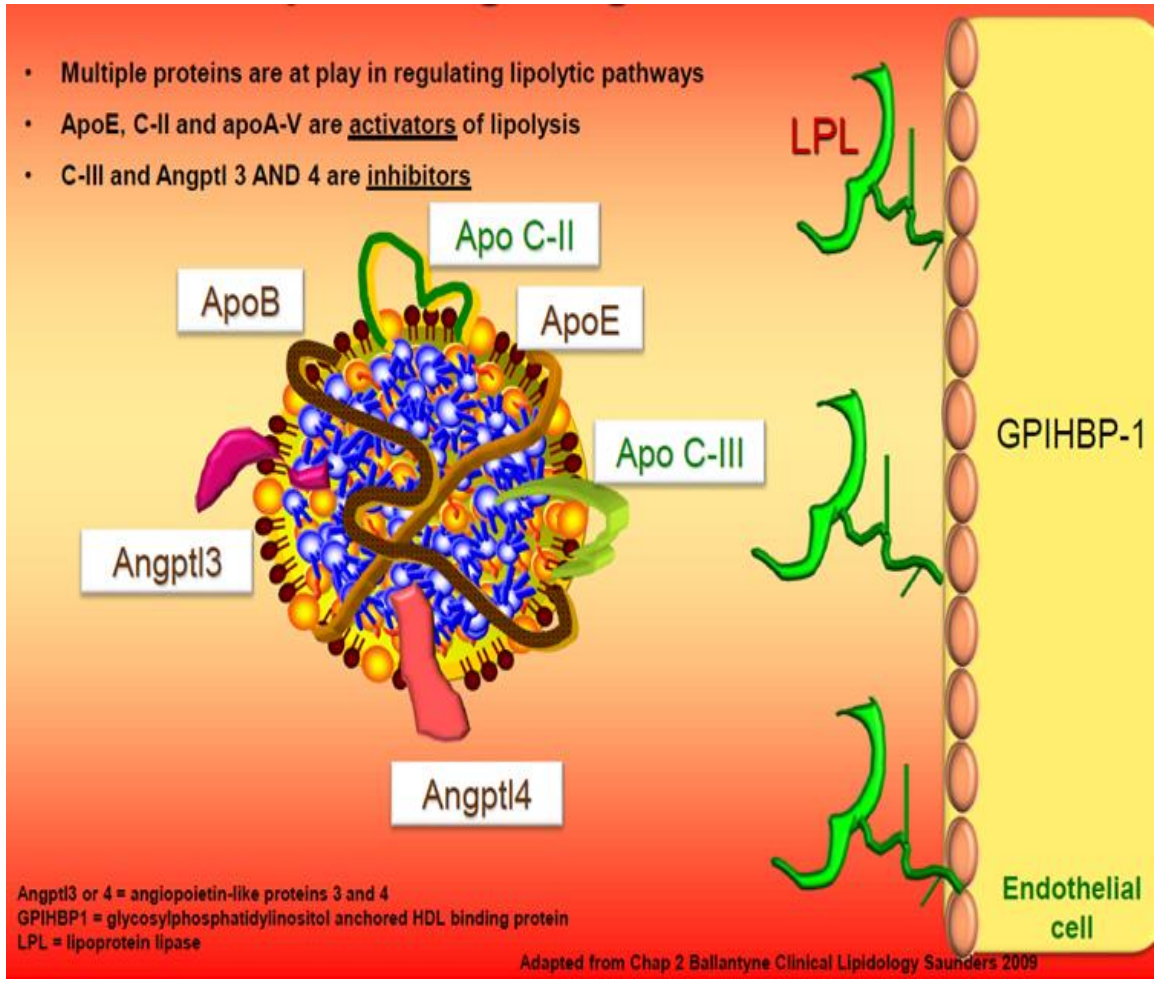
Multivariable Mendelian randomization

Analysis	variables	OR_{CHD} (95% CI)	p value
Association of apoB with risk of CHD	apoB	0.770 (0.760 - 0.781)	1.42E-170
Association of LDL-C with risk of CHD	LDL-C	0.846 (0.833 - 0.858)	8.16E-77
Association of triglycerides with risk of CHD	Triglycerides	0.815 (0.785 - 0.846)	1.37E-18
Association of LDL-C and triglycerides with risk of CHD included in same model	LDL-C	0.862 (0.849 - 0.875)	6.92E-65
	Triglycerides	0.876 (0.850 - 0.902)	1.36E-14
Association of LDL-C, triglycerides and apoB with risk of CHD included in same model	apoB	0.761 (0.723 - 0.798)	7.51E-20
	LDL-C	1.010 (0.967 - 1.055)	0.186
	Triglycerides	1.014 (0.965 - 1.065)	0.189
Association of LDL-C and apoB with risk of CHD included in same model	apoB	0.762 (0.738 - 0.787)	1.27E-36
	LDL-C	1.009 (0.977 - 1.042)	0.140
Association of triglycerides and apoB with risk of CHD included in same model	apoB	0.765 (0.751 - 0.779)	1.20E-105
	triglycerides	1.011 (0.975 - 1.048)	0.161

Ference BA, et al. JAMA. 2019;321(4):1-11. doi:10.1001/jama.2018.20045

Lowering triglycerides: genetically validated LPL pathway targets



ORIGINAL ARTICLE

Loss-of-Function Mutations in *APOC3* and Risk of Ischemic Vascular Disease

Anders Berg Jørgensen, M.D., Ph.D., Ruth Frikke-Schmidt, M.D., D.M.Sc., Børge G. Nordestgaard, M.D., D.M.Sc., and Anne Tybjærg-Hansen, M.D., D.M.Sc.

ORIGINAL ARTICLE

Genetic and Pharmacologic Inactivation of ANGPTL3 and Cardiovascular Disease

F.E. Dewey, V. Gusarova, R.L. Dunbar, C. O'Dushlaine, C. Schurmann, O. Gottesman, S. McCarthy, C.V. Van Hout, S. Bruse, H.M. Dansky, J.B. Leader, M.F. Murray, M.D. Ritchie, H.L. Kirchner, L. Habegger, A. Lopez, J. Penn, A. Zhao, W. Shao, N. Stahl, A.J. Murphy, S. Hamon, A. Bouzelmat, R. Zhang, B. Shumel, R. Pordy, D. Gipe, G.A. Herman, W.H.H. Sheu, I-T. Lee, K.-W. Liang, X. Guo, J.I. Rotter, Y.-D.I. Chen,* W.E. Kraus, S.H. Shah, S. Damrauer, A. Small, D.J. Rader, A.B. Wulff, B.G. Nordestgaard, A. Tybjærg-Hansen, A.M. van den Hoek, H.M.G. Princen, D.H. Ledbetter, D.J. Carey,* J.D. Overton, J.G. Reid, W.J. Sasiela, P. Banerjee, A.R. Shuldiner, I.B. Borecki, T.M. Teslovich, G.D. Yancopoulos, S.J. Mellis, J. Gromada, and A. Baras

ORIGINAL ARTICLE

Inactivating Variants in *ANGPTL4* and Risk of Coronary Artery Disease

Frederick E. Dewey, M.D., Viktoria Gusarova, Ph.D., Colm O'Dushlaine, Ph.D., Omri Gottesman, M.D., Jesus Trejos, M.S., Charleen Hunt, Ph.D., Cristopher V. Van Hout, Ph.D., Lukas Habegger, Ph.D., David Buckler, Ph.D., Ka-Man V. Lai, Ph.D., Joseph B. Leader, Ph.D., Michael F. Murray, M.D., Marylyn D. Ritchie, Ph.D., H. Lester Kirchner, Ph.D., David H. Ledbetter, Ph.D., John Penn, M.S., Alexander Lopez, M.S., Ingrid B. Borecki, Ph.D., John D. Overton, Ph.D., Jeffrey G. Reid, Ph.D., David J. Carey, Ph.D., Andrew J. Murphy, Ph.D., George D. Yancopoulos, M.D., Ph.D., Aris Baras, M.D., Jesper Gromada, Ph.D., D.M.Sc., and Alan R. Shuldiner, M.D.

Designing APOC3 ASO trials: Δ TG, LDL-C, non-HDL-C, or apoB?

Parameter	ISIS 304801 Monotherapy			
	Placebo (N=16)	100 mg (N=11)	200 mg (N=13)	300 mg (N=11)
Triglycerides, mg/dL				
Baseline	522.7 ±369.7	590.6 ±260.3	641.5 ±291.7	559.1 ±224.6
Median (IQR)	459 (356, 582)	558 (351, 825)	588 (464, 717)	566 (355, 702)
Endpoint	547.1 ±355.4	311.6 ±142.6	234.7 ±163.0	139.5 ±36.4 ‡
Median (IQR)	456 (343, 640)	277 (226, 394)	180 (157, 262)	120 (115, 185) ‡
% Change	20.1 ±72.0	-31.3 ±56.8*	-57.7 ±28.3†	-70.9 ±14.1‡
Non-HDL-C, mg/dL				
Baseline	208.1 ±81.7	203.9 ±53.0	208.2±60.8	175.3 ±60.6
Endpoint	198.6 ±32.2	185.8 ±49.3	180.3 ±33.6	144.1 ±56.3
% Change	6.2 ±40.0	-7.2 ±18.8	-6.8 ±17.0	-11.3 ±38.3
LS Mean ±SE	6.2 ±7.8	-6.3 ±9.3	-11.8 ±8.6	-11.7 ±9.3

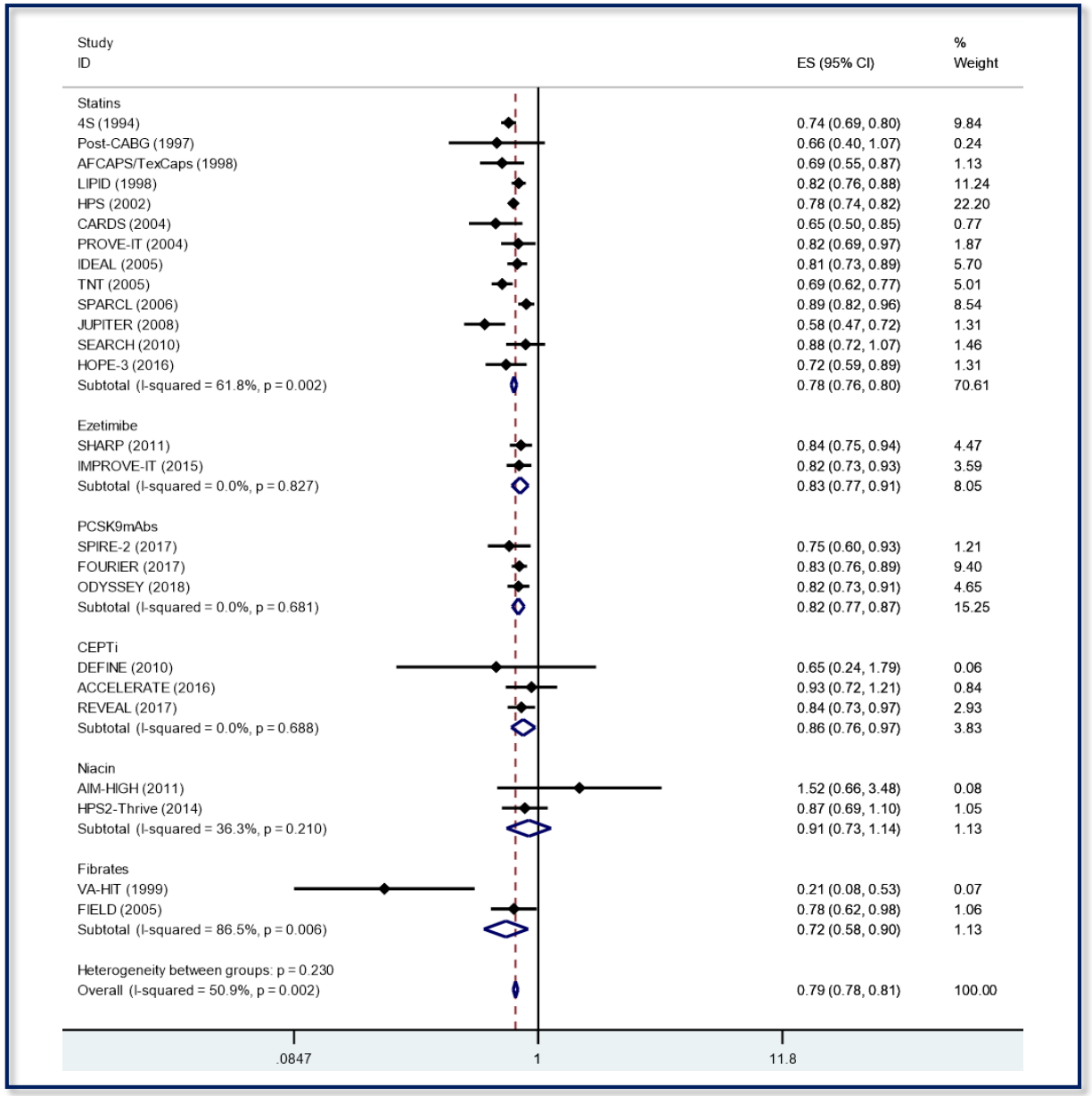
Parameter	ISIS 304801 Monotherapy			
	Placebo (N=16)	100 mg (N=11)	200 mg (N=13)	300 mg (N=11)
LDL-C, mg/dL				
Baseline	105.1 ±56.3	93.0 ±32.6	80.8 ±25.1	64.6 ±27.7
Endpoint	102.1 ±43.4	132.1 ±46.5	134.3 ±35.6	116.5 ±53.6
% Change	10.8 ±41.1	48.3 ±39.0*	79.4 ±53.3†	118.3 ±177.3*
LS Mean ±SE	10.8 ±23.0	46.9 ±25.8	72.1 ±23.7	110.6 ±25.6†
Total ApoB, mg/dL				
Baseline	117.8 ±38.8	116.3 ±26.1	114.1 ±27.5	100.0 ±20.3
Endpoint	115.2 ±23.1	116.7 ±32.4	120.5 ±21.0	101.7 ±41.9
% Change	3.9 ±26.0	0.5 ±14.9	10.2 ±18.1	1.3 ±36.2
LS Mean ±SE	3.9 ±6.3	3.6 ±7.4	7.1 ±6.9	1.5 ±7.4

Gaudet D, et al. N Engl J Med. 2015;373:438-447.

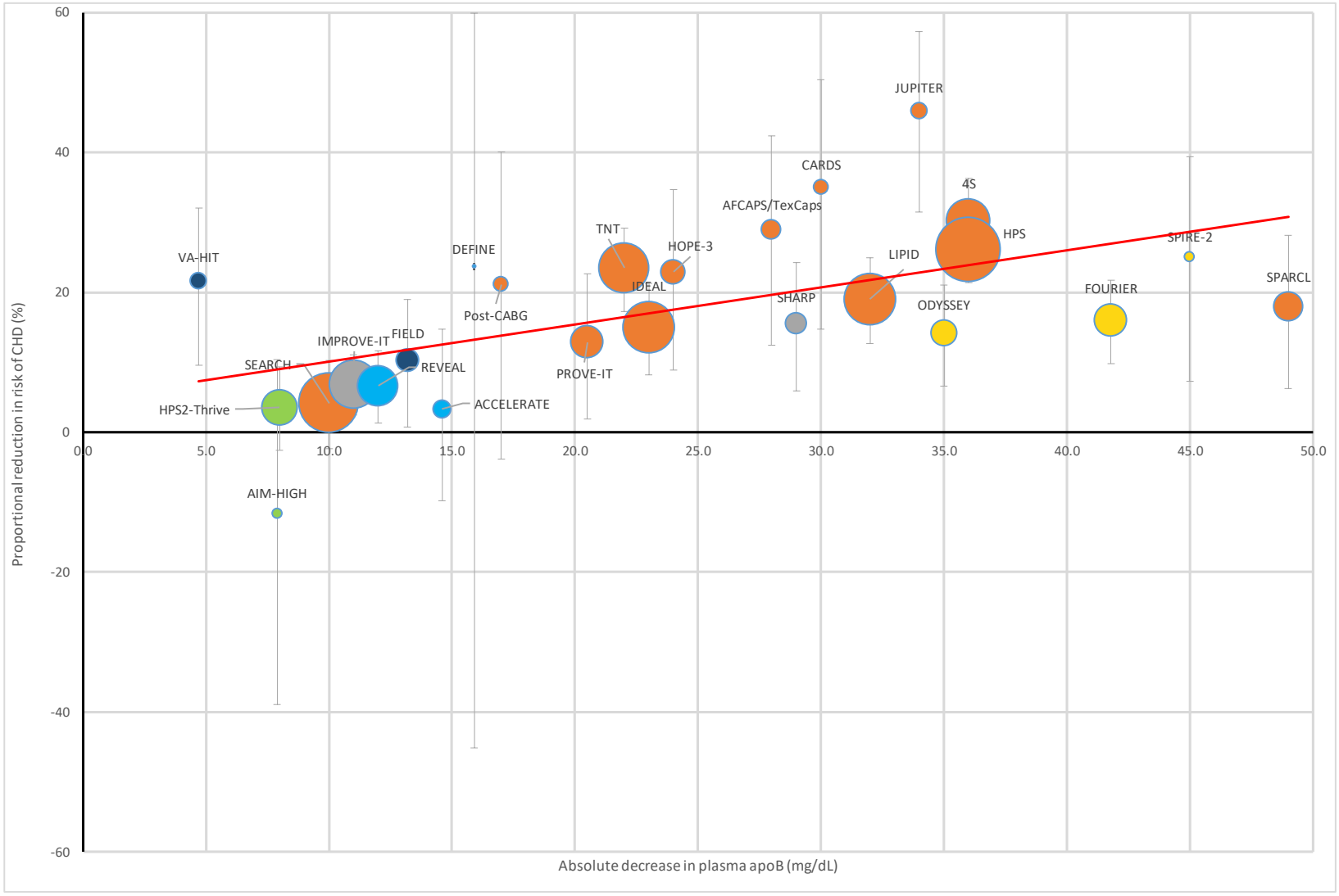
Meta-Analysis of Various Lipid lowering Therapies per unit lower apoB

- N = 25 trials (6 classes of lipid lowering therapy)
- N = 285,241 participants (mean age: 63.3 years; female sex: 24.7%)
- N = 40,244 first major cardiovascular events
- mean baseline LDL-C level = 100.7 mg/dL mean baseline apoB level = 93.9 mg/dL
- mean absolute Δ apoB between the treatment and comparison groups at one year was 24.1 mg/dL.
- overall RR per 30 mg/dL reduction in apoB 0.79 (95% CI 0.77-0.81) for major CV events

Galimberti F, Ference BA, et al. in progress

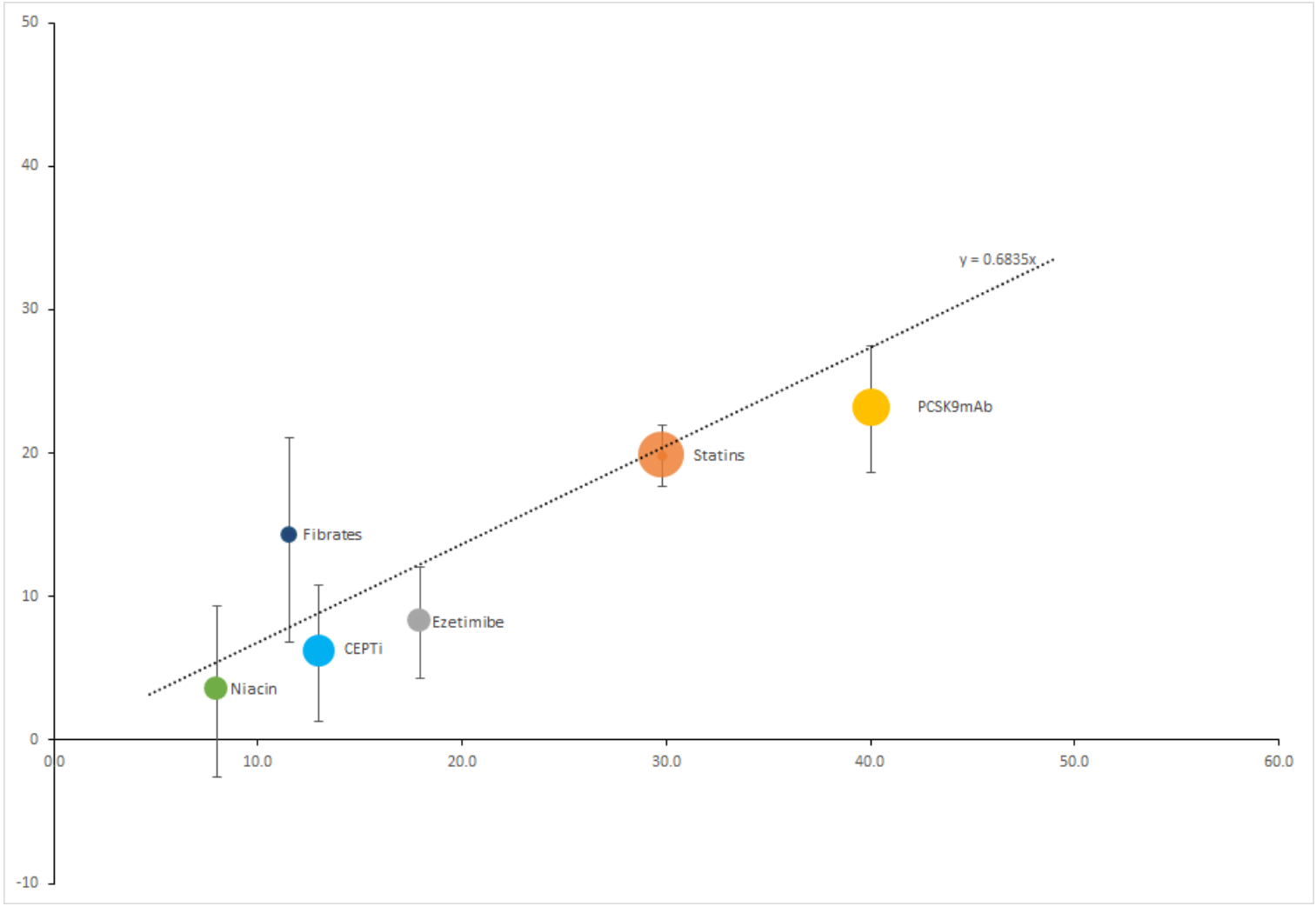


Meta-Analysis of Various Lipid lowering Therapies per unit lower apoB



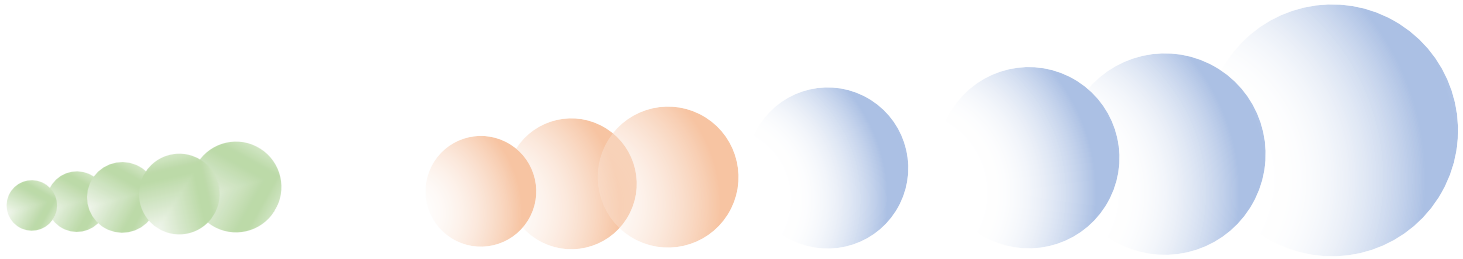
Galimberti F, Ference BA, et al. in progress

Meta-Analysis of Various Lipid lowering Therapies per unit lower apoB



Galimberti F, Ference BA, et al. in progress

How much do triglycerides need to be reduced?



Non-HDL (TC - HDL-C) = LDL-C + (Triglycerides ÷ 5)

1 mg/dL

(5 ÷ 5) = 1 mg/dL

40 mg/dL LDL-C ≈ **200 mg/dL TG**

Ference BA, et al. JAMA 2019;321(4):1-11

Conclusions

- All apoB-containing lipoproteins < 70 nm in diameter (including LDL particles, VLDL particles and their metabolic remnants) can freely flux across the endothelial barrier when they may become retained in the artery wall leading to the development and progression of an atherosclerotic plaque
- Mendelian randomization studies suggest that the causal effect of all apoB-containing lipoproteins is proportional to the absolute change in concentration of circulating particles as measured by apoB, rather than by the cholesterol or triglyceride content carried by those particles
- Meta-analysis of randomized trials suggest that the clinical benefit of any lipid lowering therapy should be proportional to the absolute change in apoB concentration, rather than the corresponding change in plasma LDL-C, triglycerides or both